HEREDITARY TRANSTHYRETIN AMYLOIDOSIS: CLINICAL CHARACTERISTICS, DIAGNOSIS AND MANAGEMENT

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Abstract

Hereditary transthyretin amyloidosis (hATTR) is an adult onset, lethal, autosomal dominant, multisystemic disease due to the deposition of mutated transthyretin (TTR) in various tissues, mainly the peripheral nerves and the heart. Circulating mutated TTR tetramers are unstable and dissociate into misfolded monomers which then polymerize into amyloid. Although there are more than 120 mutations in the TTR gene, the p.Val30Met mutation is by far the commonest and typically presents with a length dependent sensory and autonomic axonal neuropathy or a mixed phenotype that also includes cardiomyopathy. Due to its multisystemic phenomenology patients may present to non-neurologists and diagnosis can be delayed. Treatment is now available and includes TTR stabilizers as well as gene silencing therapies. Timely diagnosis is of paramount importance for a better prognosis.

Introduction

Hereditary transthyretin amyloidosis (hATTR) is an adult onset, autosomal dominant, multisystemic disease due to the deposition of misfolded mutated transthyretin (TTR) in various tissue beds [1]. Peripheral nerves and the heart are most commonly affected but clinical phenotype is variable. The TTR gene consists of four exons and is located on chromosome 18 [2]. TTR circulates as a homotetramer in plasma and each monomer consists of a 127-amino acid peptide with a predominant β-pleated sheet secondary structure. TTR is primarily synthesized by the liver (>90%), retinal pigment epithelium and the choroid plexus. In the circulation, the primary functions of TTR are to be a carrier of vitamin A, in association with the retinol binding protein, and a carrier of about 15% of thyroxine [3]. The name trans-thy-retin is derived from its function in plasma. However, an increasing number of physiological roles for TTR are being recognized both in the peripheral and central nervous systems [4].

To date, there are more than 120 TTR mutations associated with hATTR with the most common being the p.Val30Met mutation which causes predominantly a neuropathic or mixed phenotype, the latter occurring particularly in late onset patients, defined as disease onset after the age of 50 years [5]. The clinical phenotype of hATTR depends on the predominant tissue bed affected which in turn is predominantly determined, via poorly understood mechanisms, by the specific mutation. Penetrance of specific mutations may vary in different populations and is probably modulated by genetic modifiers [6].

Epidemiology

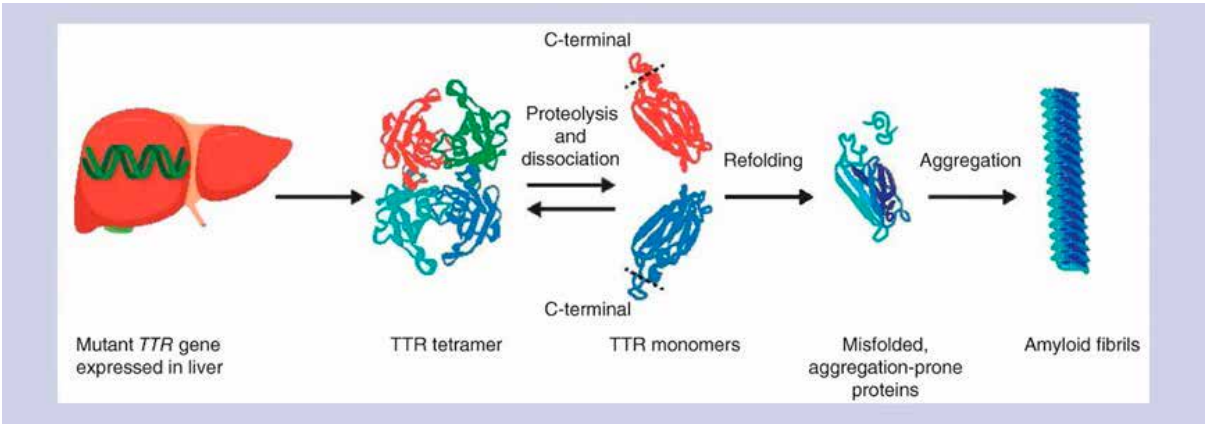
Hereditary transthyretin amyloidosis is found worldwide with major endemic foci in Northern Portugal, Sweden and Japan [7]. More recently smaller endemic regions have been identified in Cyprus and Majorca while in Greece there are several families in Crete [6, 8-10]. In most of Europe, mutations in the ATTR gene are heterogeneous while in smaller endemic foci such as Cyprus the only pathogenic mutation found so far is p.Val30Met.

Pathogenesis

ATTR circulates in plasma as homotetramer, produced and released by the liver. The tetramer naturally dissociates at a certain rate into monomers which, due to their intrinsic secondary structure, tend to misfold and polymerise into prefibrillar and fibrillar structures as amyloid (figure 1) [11]. The phenomenon of dissociation and misfolding of TTR occurs even in the absence of any mutation, as is seen in late onset ATTRw (wild type amyloidosis) cardiomyopathy [12].

In the presence of a pathogenic mutation the rate of homotetramer dissociation is increased and the misfolded monomers penetrate various tissue beds where amyloidogenesis takes place.

Figure 1. Mutated TTR increases destabilization of the homotetramer resulting in increased levels of monomers which misfold and aggregate via various intermediates into amyloid in various tissues beds (From "Patisiran, an RNAi therapeutic for the treatment of hereditary transthyretin-mediated amyloidosis" with kind permission of Future Medicine Ltd).



The mechanisms whereby specific mutations in ATTR give rise to various phenotypes is poorly understood but likely involves tissue bed protein homeostasis, mutated TTR peptide folding kinetics and chaperone protein metabolism both local and remote [13, 14]. The phenomena of variable penetrance of the p.Val30Met mutation in various populations, giving rise to the same neuropathic phenotype, as well as the phenomenon of anticipation (which is not based on a repeat nucleotide mechanism) suggests that genetic background as well as epigenetic factors may play a role. In the Cypriot and Portuguese populations complement C1Q polymorphisms impact the age of onset of the p.Val30Met mutation [6, 15, 16].There is also animal data that complement participates in amyloidogenesis and modulates disease expression [17].

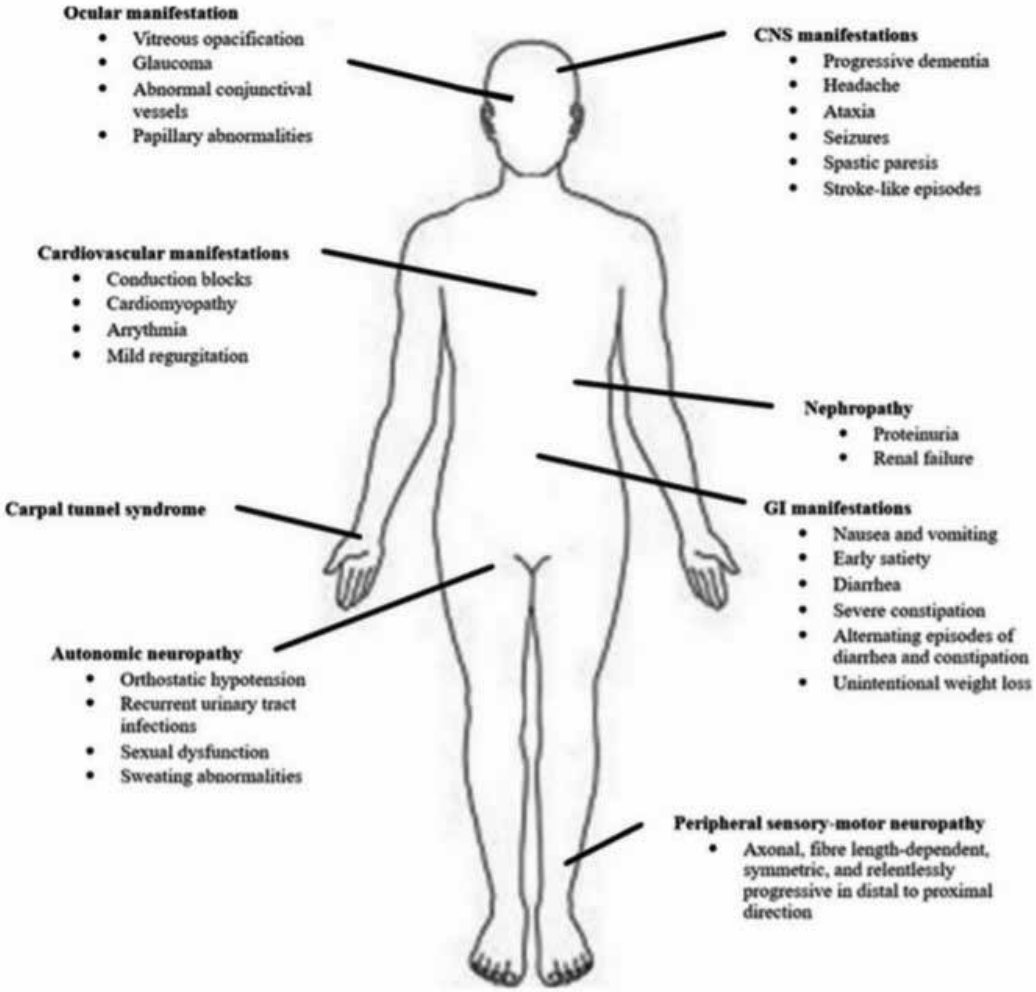
Clinical phenotypes

Hereditary transthyretin amyloidosis is a multisystemic disease with the phenotype largely dependent on the mutation and various organs can be simultaneously or sequentially involved (figure 2) [18]. There are more than 120 TTR mutations but the most common mutation worldwide is the p.Val30Met mutation. This mutation gives rise to a predominantly neuropathic phenotype and patients present with symptoms of a length dependent small fibre and autonomic neuropathy which, with the passage of time, involves large sensory and motor nerve fibres as well. Traditionally this was called Familial Amyloid Neuropathy (FAP) and was originally described in Portugal by Andrade in 1952 [19]. Early onset FAP presents before the age of 50 years and has the typical phenotype as described below. Late onset FAP has mixed features that also includes a cardiomyopathy and presents after the age of 50 years [1]. Late onset FAP is more likely to be sporadic while early onset FAP is usually familial especially in endemic areas.

Age of onset in hATTR neuropathy is variable and in familial cases anticipation is common. In both p.Val30Met and non-p.Val30Met mutations, late onset patients tend to have a more aggressive course. The typical phenotype of early onset p.Val30Met neuropathy is that of a length dependent sensorimotor and autonomic axonopathy presenting with sharp shooting pains in the feet, nausea and early satiety, change in bowel habit, diarrhoea and/or constipation, weight loss, bladder involvement, impotence, and changes in sweating, such lack of sweating in the feet and hands [1]. On examination there is dissociated sensory loss in the feet and postural hypotension is not uncommon. Sometimes, in the first twelve months of symptom onset, clinical examination may not be unequivocally abnormal, in which case quantitative sensory testing and/or Sudoscan testing may be carried out for small diameter and autonomic fibre assessment [20]. In the author's experience inserting the tuning fork in a glass of iced water and comparing perception of coldness on the dorsum of foot, mid shin and knee is quite a reliable and practical way to pick up small fibre dysfunction. It is important not simply to ask if the coldness can be felt but also how quickly it is appreciated at each level in the leg. Furthermore, temperature appreciation tends to be more affected than pain sensation with touch and joint position involved later by which time muscle wasting and weakness sets in (figures 3a and 3b).

It is crucial to think of hATTR neuropathy to diagnose it. In this respect a careful family history is paramount and should also include enquiry for less typical symptoms such as carpal tunnel syndrome,

Figure 2. Multisystem involvement in hATTR. The TTR mutation as well a disease duration determines the clinical phenotype (From "Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: Current Perspectives on Improving Patient Care" with kind permission of Dovepress)



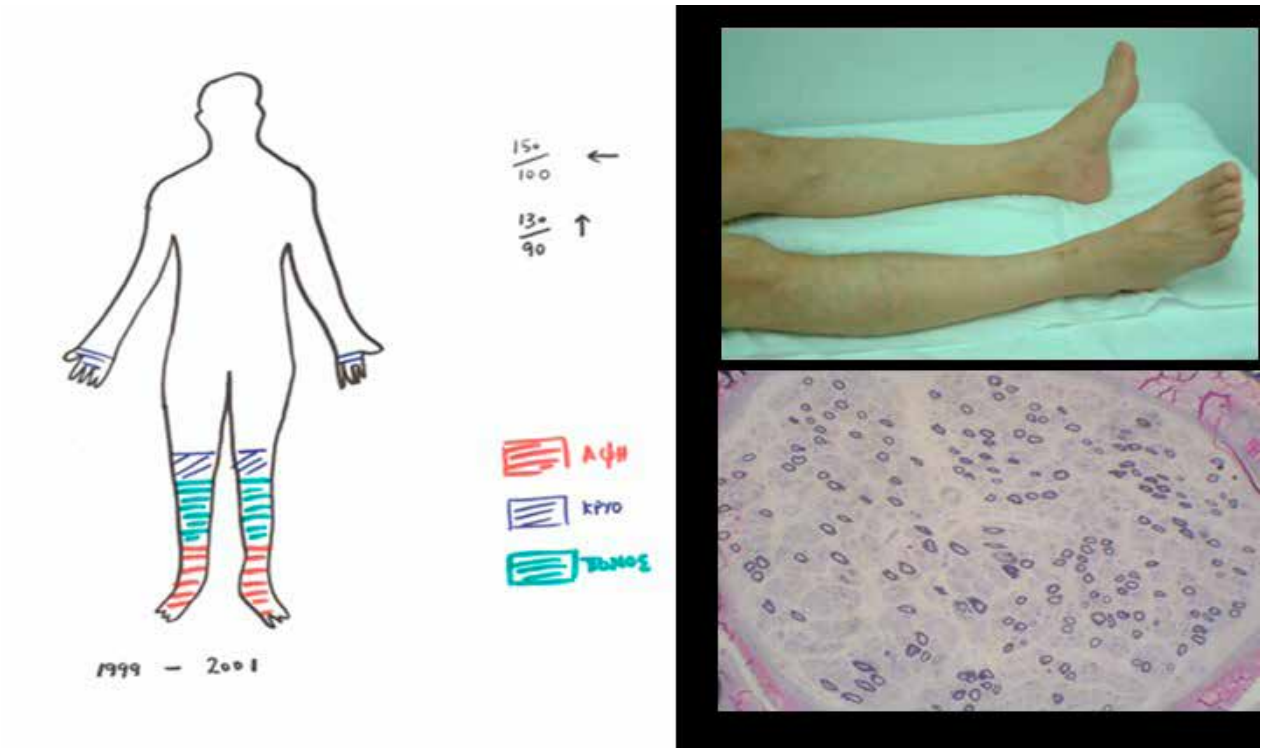
lumbar canal stenosis, biceps tendon rupture and cardiomyopathy in the family.

One of the authors has personal experience of patients misdiagnosed as Crohn's disease, irritable bowel syndrome, Charcot foot, sick-sinus syndrome needing a pacemaker and recurrent urinary tract infections due to a neurogenic bladder. All of these patients, in retrospect, had a family history of hATTR neuropathy but perhaps more importantly they all had dissociated sensory loss which was not recognized at the time of their first presentation. In fact, it is not uncommon that patients with hATTR neuropathy take several years to be diagnosed especially sporadic cases in non-endemic areas.

As a result of liver transplantation, and disease survival in p.Val30Met neuropathy has increased, further manifestations of this mutation have become apparent such an eye disease and central nervous system (CNS) complications [6, 21-24]. In the Cypriot cohort of liver transplanted patients, the prevalence of ocular, cardiac and central nervous complications are 60%, 20% and 16% respectively [6].

The ocular and CNS manifestations are due to the production of mutated TTR by the retinal epithelium and ciliary body in the eye and choroid plexus and ependymal cells in the brain respectively. Ocular complications include scalloped pupils, kerato-conjunctivitis sicca, vitreous opacities and glaucoma [22]. CNS complications occur after a mean of 16 years following liver transplantation and all patients also have ocular involvement, mainly glaucoma [21]. The most commonly reported transient focal neurological episode (TFNE) in the Cypriot cohort was expressive dysphasia, followed by dysarthria, facial distortion, and unilateral limb numbness. The TFNEs tend to be stereotyped in phenomenology but not in duration in any individual patient. In some patients different hemispheres are involved. Rarely, more than one TFNE could occur in the same patient on the same day after a period of recovery. The tempo of the onset to peak

Figure 3A. Patient diagnosed three years after onset. Dissociated sensory loss with temperature (red) > pain (blue) > touch (green) loss and no significant muscle wasting. Sural nerve biopsy shows severe loss of small myelinated fibres and to a lesser degree large myelinated fibres. Years correspond to time from symptom onset to diagnosis



for TFNEs varies over several minutes and are alike conventional transient ischemic attacks [21]. In the Cypriot cohort of patients with CNS complications there was 30% mortality due to cerebral haemorrhage (figure 4).

It is worth mentioning that there are certain mutations in hATTR amyloidosis that preferentially cause oculoleptomingeal amyloidosis early in their presentation such as the Ala25Thr and Tyr69His mutations [25, 26].

As has been mentioned genotype mainly determines phenotype but age at onset, duration of disease, genetic background and epigenetic factors probably modulate phenotype (table 1) [18]. Some variants, such as p.Val122Ile, p.Ile68Leu, p.Thr60Ala and p.Leu111Met, cause a predominant cardiomyopathy presentation known as Familial Amyloid Cardiomyopathy (FAC).

Cardiac amyloidosis is not prominent in early onset p.Val30Met mutation although cardiac conduction block can occur and patients are usually inserted a pacemaker prior to liver transplantation.

FAC is an infiltrative restrictive cardiomyopathy characterized by heart failure with preserved ejection fraction, a speckled appearance on ECHO and apical sparing [12]. Numerically ATTRw cardiomyopathy is more important and is increasingly recognized as it is now treatable [27]. It should be suspected in men, aged >70 years with a cardiomyopathy and a history of carpal tunnel syndrome, lumbar spinal stenosis and biceps tendon tear.

Lastly, renal involvement is not an early feature of the p.Val30Met mutation but can occur later on in the course of the disease due to amyloid deposition and in, liver transplanted patients, due to drugs [28].

Diagnosis

In endemic regions, where family history is often present, and the family members are themselves aware of the common symptoms, diagnosis is straight forward and confirmed with clinical examination and DNA testing. In endemic regions, there are amyloid clinics where confirmed carriers are followed up and diagnosis is often made in less than a year from symptom onset. The situation is more difficult in non-endemic areas where there may be more late onset cases with uninformative family history and less typical symptoms which may delay diagnosis for years. In the case of the p.Val30Met mutation late onset cases may exhibit less autonomic involvement and more likely to exhibit cardiomyopathy or less typical features such as carpal tunnel symptoms, lumbar canal stenosis and biceps tendon rupture. It is useful to keep in mind the multisystemic involvement of

Figure 3B. Patient diagnosed eight years after onset. Dissociated sensory loss, extending almost throughout the body, severe muscle wasting in the limbs, catheterised due a neurogenic bladder. Systolic pressure was none recordable on standing up. Sural nerve biopsy (semithin section) shows severely depleted of nerve fibres of all sizes and replaced by amorphous material consisting of amyloid. Years correspond to time from symptom onset to diagnosis

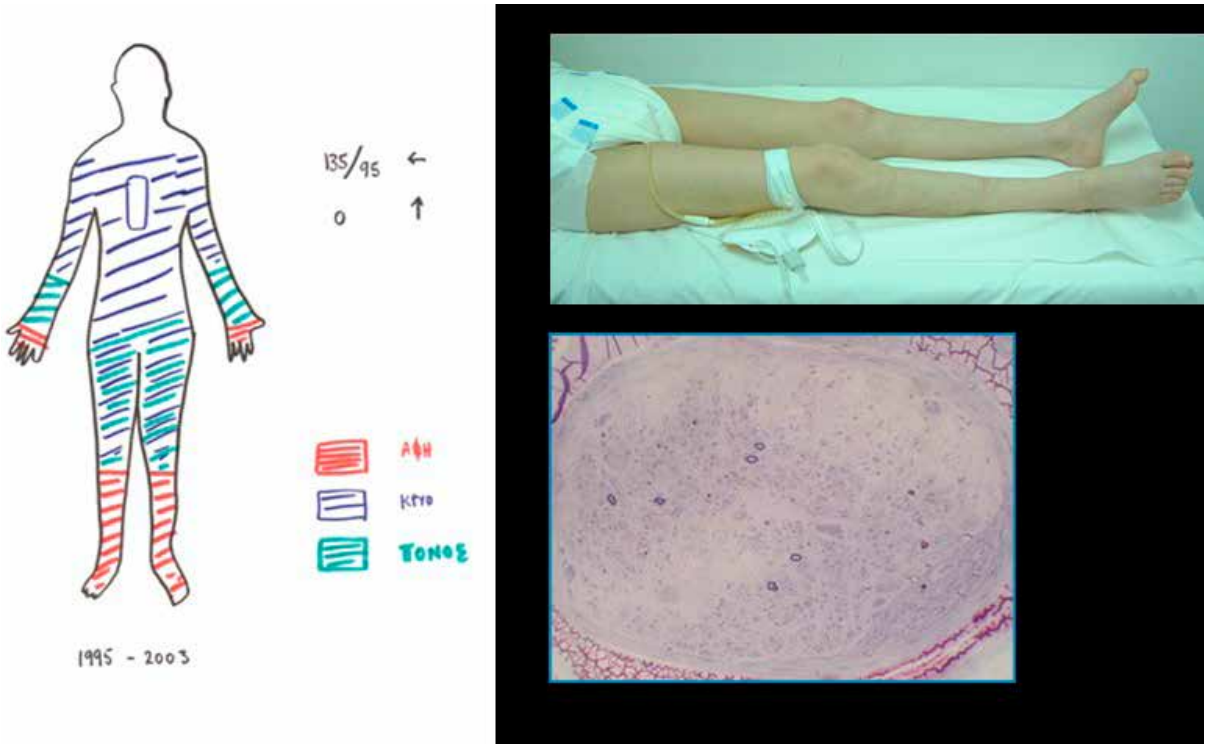
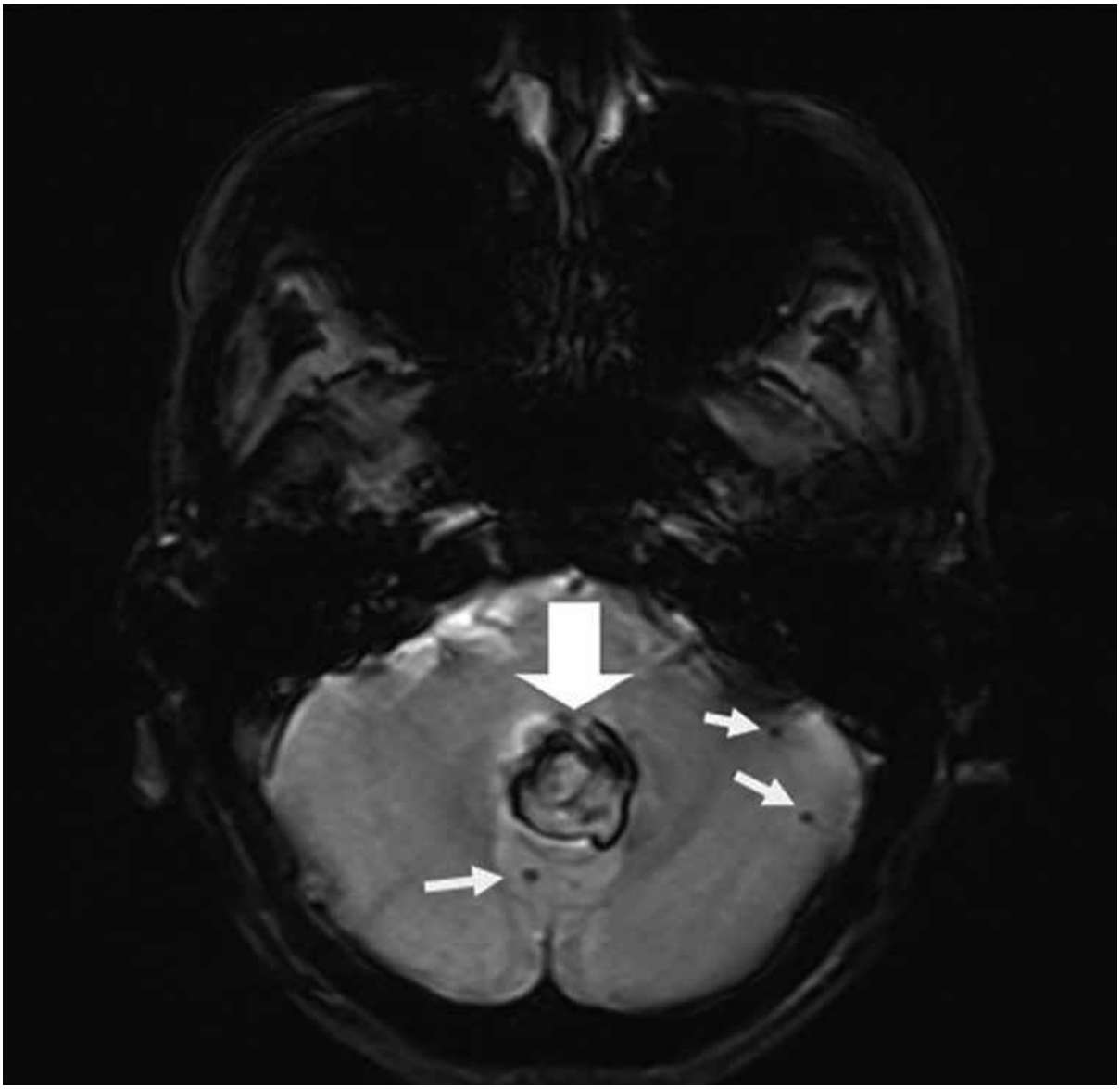


Table 1. Genotype is the main determinant of phenotype (From Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: Current Perspectives on Improving Patient Care with kind permission of Dovepress)

Mutation	Epidemiology	Peripheral Neuropathy	Autonomic Neuropathy	Cardomyopathy	Ocular Involvement	Gastrointestinal Involvement	Renal Involvement
Val30Met (early onset)	Portugal, Brazil	++	+++	±	+	++	+
Val30Met (late onset)	Japan, Sweden, USA, Italy, France	+++	+	++	+	+	±
Val122Ile	USA	±	±	+++	±	±	±
Thr60Ala	UK, USA	+	+	+++	±	±	±
Glu89Gln	Italy, Bulgaria	++	++	++	±	+	±
Ser50Arg	Japan, France, Italy, Usa	+++	+++	±	±	+	±
Phe64Leu	USA, Italy	++	++	++	±	+	±
Ile68Leu	Germany, Italy	±	±	+++	±	±	±
Ser77Tyr	USA, France, Israel	++	++	++	±	+	±
Ile107Val	USA, France, Brazil	++	++	++	±	±	±
Asp38Ala	Japan	++	++	++	±	±	±

Notes: The number of "+" provides an indication of the likelihood of presence of symptoms, with "±" indicating an unknown likelihood as the symptom is present in some patients and not in others.

Figure 4. Gradient Echo (GRE) sequence MRI, demonstrating microhemorhages (small arrows) and the major hemorrhage (big arrow) in the cerebellum (from The frequency of central nervous system complications in the Cypriot cohort of ATTRV30M neuropathy transplanted patients with kind permission of Springer nature)



hATTR amyloidosis particularly in patients presenting with peripheral neuropathies of unknown origin and be aware that diabetes mellitus can be a distractor.

In familial cases the presence of the typical symptoms and signs and confirmation of the endemic TTR gene mutation are often adequate for diagnosis. Ideally, confirmation of amyloid deposits, preferably in symptomatic tissue, with the demonstration of the typical apple green birefringence under polarized light with the Congo red stain is desirable. Biopsies can be obtained from abdominal fat, rectal mucosa, labial salivary glands, skin, nerve or myocardium [29]. The sensitivity of biopsy is variable (up to 80%) and depends on local expertise but one should bear in mind that amyloid deposition is often patchy. If biopsy is positive for amyloid then the precursor protein should be typed by immunohistochemistry or mass spectroscopy. If biopsy is negative and suspicion is high then then TTR sequencing should be carried out.

For peripheral neuropathy nerve conduction studies (NCS) may be performed but the reader should keep in mind that conventional NCS assess myelinated nerve fibers larger than eight microns. Small fibre neuropathy can be diagnosed with skin biopsy while the Sudoscan is increasingly used to assess sudomotor fibres. The latter is very easy to perform and can be done periodically in patients with symptoms suggestive of small fibre sensory and autonomic neuropathy [20].

For patients with possible infiltrative cardiomyopathy, cardiac ECHO with strain imaging looking for the speckled pattern as well as magnetic resonance imaging are useful [12]. The use of scintigraphy with bone markers such ^{99m}Tc-2,3-dicarboxypropane-1,1-diphosphonate (DPD), ^{99m}Tchydroxymethylene diphosphonate (HMDP) or ^{99m}Tcpyrophosphate (PYP) is becoming more popular due to its non-invasiveness and good specificity [30]. In the p.Val30Met mutation conduction abnormalities is an early sign and Holter monitoring has an important role. Similarly in monitoring for incipient cardiac failure, N-terminal prohormone (NT-proBNP) is very useful in the context of heart failure with preserved ejection fraction [12].

Treatment

Treatment in hATTR amyloidosis aims at eliminating the source of mutated TTR and stabilizing TTR in the circulation so that there is no further dissociation and deposition of misfolded TTR peptides in the various organs. Secondly since hATTR amyloidosis is a multisystemic disease symptomatic treatment needs to be provided by a multidisciplinary team. The multidisciplinary team will need to include among others; a gastroenterologist and dietitian, a cardiologist, an ophthalmologist, a renal physician and a neurologist.

Liver transplantation was first performed for hATTR amyloidosis in 1990 since liver is the main site of TTR production (accounts for 99% of circulating TTR) [31]. Although the transplanted liver produces normal TTR, this may continue to be deposited in previously seeded tissues such as the heart. Nevertheless life survival at 20 years after transplantation is 55% compared to 10 years life survival after disease onset due to the p.Val30Met mutation [32]. Late onset p.Val30Met mutation and non- p.Val30Met mutation do worse than early onset p.Val30Met mutation. Liver transplantation however has recently been abandoned following the introduction of TTR stabilizers and gene silencing therapies.

Oral TTR stabilizers, include Tafamidis and the non-steroidal anti-inflammatory drug Diflunisal, both of which dock into one of the carrier sites of the TTR tetramer, stabilize it and reduce the dissociation rate of the homotetramer. Less dissociation of the tetramer results in less misfolded monomers and reduced amyloid formation in the various organs. Phase 3 trials that have included both p.Val30Met and non-p.Val30Met mutations have shown reduction in neuropathy progression in most but not all patients [33, 34]. Advanced neuropathy and/or old age were bad prognostic factors for a good response.

Tafamidis, both at 20mg and 80mg, have been shown to reduce mortality and cardiovascular-related admissions in patients with hATTR and ATTRw cardiomyopathy with the latter dose been the most effective [35, 36].

Recently two gene silencing therapies have been approved for downregulating, by more than 80%, TTR production in the liver. The first is Patisiran which consists of a small interfering RNA (RNAi), encapsulated in lipid nanoparticles, given intravenously every three weeks and taken up by liver hepatocytes. Patisiran mediates the degradation of TTR mRNA in the cytoplasm. The APOLLO trial was a phase 3 study double blind trial of Patisiran, lasting 18 months that included patients with p.Val30Met mutations of both early and late onset as well as non p.Val30Met mutations. The Patisiran treated patients had a significant improvement in their mNIS+7 score (modified Neuropathy Impairment Score), a score that combines both clinical and neurophysiological neuropathy related measurements, compared to worsening in the placebo treated patients [37]. A number of quality of life measures also improved in the treated but worsened in the untreated group. A 12-month follow up study to APOLLO has confirmed both safety and effectiveness of Patisiran [38]. A substudy of APOLLO, examining the effect of Patisiran on cardiomyopathy showed a halt or even a reversal in the progression of cardiomyopathy [39].

Inotersen, the second approved gene silencing therapy, is an antisense oligonucleotide administered subcutaneously three times a week in the first week and then once weekly. The mechanism of action is to destroy the TTR RNA transcript in the nucleus through a RNase H1 mechanism[40]. Again, the treatment group fared better than the control group on the mNIS+7 as well as quality of life assessments. There were two serious adverse events in the treatment group which were glomerulonephritis and thrombocytopenia which occurred in 3% of patients each.

Patients on three weekly Patisiran are subjected to regular intravenous steroids while those on weekly subcutaneous Inotersen are exposed to potentially serious side-effects. Thus gene silencing using these two molecules lifelong is not without risks. Recently, an alternative to mRNA targeting-based gene silencing has been tested in a phase 1 study using the clustered regularly interspaced short palindromic repeats and associated Cas9 endonuclease (CRISPR-Cas9) system to achieve in vivo knock out of the transthyretin gene. Serum TTR was reduced by 87% by day 28 with the higher dose used. Admittedly only six patients with ATTR amyloid neuropathy were included and follow up data were very short but experiments on non-human primates show sustained TTR reduction for up to 360 days [41].

Conclusion

ATTR amyloidosis is an excellent example of the tri-

umph of translational medicine in neurology, whereby progress in molecular medicine actually translates into saving lives. ATTR neuropathies, a worldwide autosomal dominant multisystemic disease, with a life span of ten years, is now treatable by a variety of approaches involving gene silencing either via RNA editing or direct DNA silencing of the TTR gene. Wildtype ATTR cardiomyopathy, a much commoner condition, is similarly treatable with TTR stabilizers and also probably, with the gene silencers although further studies are needed. There are however, several unmet needs that escape effective treatment in ATTR amyloidosis and these include the eye and CNS complications of ATTR amyloidosis. These manifestations are becoming an increasing cause of morbidity and mortality since the above therapies do not impact on these privileged tissue sites. Perhaps other modes of delivery may be needed but there is certainly scope for optimism.

References

[1] Plante-Bordeneuve V, Said G. Familial amyloid polyneuropathy. *Lancet Neurol.* 2011;10:1086-1097.

[2] Tsuzuki T, Mita S, Maeda S, et al. Structure of the human prealbumin gene. *J Biol Chem.* 1985;260:12224-12227.

[3] Liz MA, Coelho T, Bellotti V, et al. A Narrative Review of the Role of Transthyretin in Health and Disease. *Neurol Ther.* 2020;9:395-402.

[4] Magalhaes J, Eira J, Liz MA. The role of transthyretin in cell biology: impact on human pathophysiology. *Cell Mol Life Sci.* 2021;78:6105-6117.

[5] Saraiva MJ, Birken S, Costa PP, et al. Family studies of the genetic abnormality in transthyretin (prealbumin) in Portuguese patients with familial amyloidotic polyneuropathy. *Ann N Y Acad Sci.* 1984;435:86-100.

[6] Andreou S, Panayiotou E, Michailidou K, et al. Epidemiology of ATTRV30M neuropathy in Cyprus and the modifier effect of complement C1q on the age of disease onset. *Amyloid.* 2018;25:220-226.

[7] Schmidt HH, Waddington-Cruz M, Botteman MF, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle Nerve.* 2018;57:829-837.

[8] Dardiotis E, Koutsou P, Papanicolaou EZ, et al. Epidemiological, clinical and genetic study of familial amyloidotic polyneuropathy in Cyprus. *Amyloid.* 2009;16:32-37.

[9] Kavousanaki M, Tzagournissakis M, Zaganas I, et al. Liver Transplantation for Familial Amyloid Polyneuropathy (Val30Met): Long-Term Follow-up Prospective Study in a Nontransplant Center. *Transplant Proc.* 2019;51:429-432.

[10] Reines JB, Vera TR, Martin MU, et al. Epidemiology of transthyretin-associated familial amyloid polyneuropathy in the Majorcan area: Son Llatzer Hospital descriptive study. *Orphanet J Rare Dis.* 2014;9:29.

[11] Kristen AV, Ajroud-Driss S, Conceicao I, et al. Patisiran, an RNAi therapeutic for the treatment of hereditary transthyretin-mediated amyloidosis. *Neurodegener Dis Manag.* 2019;9:5-23.

[12] Bistola V, Parissis J, Foukarakis E, et al. Practical recommendations for the diagnosis and management of transthyretin cardiac amyloidosis. *Heart Fail Rev.* 2021;26:861-879.

[13] Buxbaum JN, Tagoe C, Gallo G, et al. Why are some amyloidoses systemic? Does hepatic "chaperoning at a distance" prevent cardiac deposition in a transgenic model of human senile systemic (transthyretin) amyloidosis? *FASEB J.* 2012;26:2283-2293.

[14] Sekijima Y, Wiseman RL, Matteson J, et al. The biological and chemical basis for tissue-selective amyloid disease. *Cell.* 2005;121::73-85.

[15] Dardiotis E, Koutsou P, Zamba-Papanicolaou E, et al. Complement C1Q polymorphisms modulate onset in familial amyloidotic polyneuropathy TTR Val30Met. *J Neurol Sci.* 2009;284:158-162.

[16] Dias A, Santos D, Coelho T, et al. C1QA and C1QC modify age-at-onset in familial amyloid polyneuropathy patients. *Ann Clin Transl Neurol.* 2019;6:748-754.

[17] Panayiotou E, Fella E, Papacharalambous R, et al. C1q ablation exacerbates amyloid deposition: A study in a transgenic mouse model of ATTRV30M amyloid neuropathy. *PLoS One.* 2017;12:e0175767.

[18] Luigetti M, Romano A, Di Paolantonio A, et al. Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: Current Perspectives on Improving Patient Care. *Ther Clin Risk Manag.* 2020;16:109-123.

[19] Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain.* 1952;75:408-427.

[20] Castro J, Miranda B, Castro I, et al. The diagnostic accuracy of Sudoscan in transthyretin familial amyloid polyneuropathy. *Clin Neurophysiol.* 2016;127:2222-2227.

[21] Dardiotis E, Andreou S, Aloizou AM, et al. The frequency of central nervous system complications in the Cypriot cohort of ATTRV30M neuropathy transplanted patients. *Neurol Sci.* 2020;41:1163-1170.

[22] Buxbaum JN, Brannagan T, 3rd, Buades-Reines J, et al. Transthyretin deposition in the eye in

the era of effective therapy for hereditary ATTRV30M amyloidosis. *Amyloid.* 2019;26:10-14.
[23] Sekijima Y, Yazaki M, Oguchi K, et al. Cerebral amyloid angiopathy in posttransplant patients with hereditary ATTR amyloidosis. *Neurology.* 2016;87:773-781.
[24] Maia LF, Magalhaes R, Freitas J, et al. CNS involvement in V30M transthyretin amyloidosis: clinical, neuropathological and biochemical findings. *J Neurol Neurosurg Psychiatry.* 2015;86:159-167.
[25] Ziskin JL, Greicius MD, Zhu W, et al. Neuropathologic analysis of Tyr69His TTR variant meningovascular amyloidosis with dementia. *Acta Neuropathol Commun.* 2015;3:43.
[26] Hagiwara K, Ochi H, Suzuki S, et al. Highly selective leptomeningeal amyloidosis with transthyretin variant Ala25Thr. *Neurology.* 2009;72:1358-1360.
[27] Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2021;42:1554-1568.
[28] Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. *Clin J Am Soc Nephrol.* 2012;7:1337-1346.
[29] Adams D, Suhr OB, Hund E, et al. First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol.* 2016;29 Suppl 1:S14-26.
[30] Pilebro B, Suhr OB, Naslund U, et al. (99m)Tc-DPD uptake reflects amyloid fibril composition in hereditary transthyretin amyloidosis. *Ups J Med Sci.* 2016;121:17-24.
[31] Holmgren G, Steen L, Ekstedt J, et al. Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met30). *Clin Genet.* 1991;40:242-246.
[32] Ericzon BG, Wilczek HE, Larsson M, et al. Liver Transplantation for Hereditary Transthyretin Amyloidosis: After 20 Years Still the Best Therapeutic Alternative? *Transplantation.* 2015;99:1847-1854.
[33] Coelho T, Maia LF, Martins da Silva A, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology.* 2012;79:785-792.
[34] Berk JL, Suhr OB, Obici L, et al. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA.* 2013;310:2658-2667.
[35] Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med.* 2018;379:1007-1016.
[36] Damy T, Garcia-Pavia P, Hanna M, et al. Efficacy and safety of tafamidis doses in the Tafamidis in Transthyretin Cardiomyopathy Clinical Trial (ATTR-ACT) and long-term extension study. *Eur J Heart Fail.* 2021;23:277-285.
[37] Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *N Engl J Med.* 2018;379:11-21.
[38] Adams D, Polydefkis M, Gonzalez-Duarte A, et al. Long-term safety and efficacy of patisiran for hereditary transthyretin-mediated amyloidosis with polyneuropathy: 12-month results of an open-label extension study. *Lancet Neurol.* 2021;20:49-59.
[39] Solomon SD, Adams D, Kristen A, et al. Effects of Patisiran, an RNA Interference Therapeutic, on Cardiac Parameters in Patients With Hereditary Transthyretin-Mediated Amyloidosis. *Circulation.* 2019;139:431-443.
[40] Benson MD, Dasgupta NR, Monia BP. Inotersen (transthyretin-specific antisense oligonucleotide) for treatment of transthyretin amyloidosis. *Neurodegener Dis Manag.* 2019;9:25-30.
[41] Gillmore JD, Gane E, Taubel J, et al. CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis. *N Engl J Med.* 2021;385:493-502.