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Clinical and Genetic Evaluation of People with or at Risk of Hereditary ATTR Amyloidosis: An Expert Opinion and Consensus on Best Practice in Ireland and the UK

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COMMENTARY

Clinical and Genetic Evaluation of People with or at Risk of Hereditary ATTR Amyloidosis: An Expert Opinion and Consensus on Best Practice in Ireland and the UK

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ABSTRACT

Hereditary transthyretin-mediated amyloidosis (hATTR) is challenging to diagnose early owing to the heterogeneity of clinical presentation, which differs according to the *TTR* gene variant and its penetrance in each individual. The TTR variants seen most frequently in the UK and Ireland (T80A, V142I and V50M) differ to those commonly occurring in other geographic locations and warrant a specific consideration for diagnosis and genetic testing. In addition, recent availability of treatment for this condition has reinforced the need for a more consistent approach to the management of patients, including access to specialist services, genetic testing and counselling, and clinical investigation for families living in the UK and Ireland. A multidisciplinary panel of experts from the UK and Ireland was convened to identify the cur-

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rent challenges, provide recommendations, and develop a consensus for the diagnosis and screening of people with, or at risk of, hATTR. Over a series of meetings, experts shared their current practices and drafted, refined and approved a consensus statement. This consensus statement provides recommendations for three different groups: (1) people with symptoms raising a possibility of hATTR amyloidosis; (2) people with biopsy-confirmed hATTR amyloidosis; and (3) people without symptoms who may have hATTR amyloidosis (i.e. relatives of people with identified TTR variants). For each group, recommendations are made for the required steps for the diagnosis and follow-up of symptomatic patients, and for guidance on the specialist support for counselling and pre-symptomatic genetic testing of at-risk individuals. This guidance is intended to be practical and based on available evidence. The aim is for regional amyloid specialist centres to provide timely diagnosis, clinical screening, and treatment for individuals and their families with hATTR amyloidosis.

Keywords: Hereditary transthyretin amyloidosis; ATTR; Genetic screening; Expert opinion

Key Summary Points

An expert consensus statement on best practice for genetic diagnosis, clinical screening and management of individuals with, or at risk of, hATTR amyloidosis has been proposed to encourage a consistent approach to patient management in different regions of the UK and Ireland.

Recommendations were made for three different groups: (1) people with symptoms raising a possibility of hATTR amyloidosis; (2) people with biopsy-confirmed ATTR amyloidosis; and (3) people without symptoms who may have hATTR amyloidosis (i.e. relatives of people with identified TTR variants).

The recommendations outlined in this statement may help increase the identification of affected individuals, help them gain access to regular follow-up and, if needed, treatment to reduce disease progression once they become symptomatic.

INTRODUCTION

Hereditary transthyretin-mediated amyloidosis (hATTR), also known as ATTRv (v for variant), is a rare, adult-onset, autosomal-dominant disorder, caused by heterozygous pathogenic variants in the transthyretin *TTR* gene [1–3]. It is a multisystem disorder caused by the extracellular deposition of amyloid, derived from transthyretin, which progressively impairs the function of multiple tissues and organs culminating in increasing disability and death within 3–15 years of symptom onset [1–8].

The disease manifests with either predominantly axonal sensory, motor and autonomic neuropathies, or as an infiltrative cardiomyopathy [9]. Many patients have disease affecting both the nerves (neuropathy) and heart (cardiomyopathy) and occasionally other organs, such as the kidneys and eyes [2, 10–13]. This heterogeneity, which differs according to TTR variant and its penetrance in each individual [3], makes the diagnosis of hATTR amyloidosis challenging, particularly in non-endemic regions, where patients often present with no known family history [9, 10].

TTR gene variants in the UK and Ireland differ to those commonly occurring in other geographic locations [14–17] (see Table 1 for a list of common variants in the UK and Ireland) and may warrant a unique approach with regards to screening and evaluation compared with other regions. The National Amyloidosis Centre (NAC) in London is a centrally funded National Health Service specialist unit available to patients from England, Scotland, Northern Ireland, Wales and the Republic of Ireland. The NAC provides both clinical and genetic

Table 1 Common hATTR amyloidosis pathogenic variants in Ireland and the UK

Common pathogenic variant in UK and Ireland	cDNA variant	Endemic region/ penetrance	Predominant phenotype	'Red flag' signs	Suggested baseline tests and investigations	Predicted age of symptom onset (years)
T80A	c.238 A>G	Ireland	Mixed/CM/ PN	CTS/ AN	Tc-DPD/CMR Neurologist	> 50
V50M early	c.148G>A	Portugal	PN/AN	AN/ PN	Neurologist	> 20
V50M late	c.148G>A	Widespread/ low	Mixed	–	Tc-DPD/CMR Neurologist	> 50
V142I	c.424G>A	Africa/low	CM	CTS	Tc-DPD/CMR	> 50
G67V	c.200 C>T	Unknown/ high	Mixed	–	Tc-DPD/CMR	> 30
S97Y	c.290C>A	Unknown/ unknown	Mixed	–	Neurologist Tc-DPD/CMR	> 50

AN autonomic neuropathy (dysautonomia), *CM* cardiomyopathy, *CMR* cardiac magnetic resonance imaging, *CTS* carpal tunnel syndrome, *PN* polyneuropathy, *Tc-DPD* technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid imaging

diagnostic services. Despite this central facility, there is variance across the UK and Ireland with regards to the identification, diagnosis and monitoring of patients with, or at risk of, hATTR amyloidosis. Furthermore, with hATTR amyloidosis treatments typically being more effective if initiated at the early stages of disease [18, 19], there is a need to provide timely and equitable access to specialist healthcare services, genetic testing and counselling, and clinical investigation for families living in different regions of the UK and Ireland. Although patient support is available through the UK ATTR Amyloidosis Patients Association (http://ttramyloidosis.uk/), there are still challenges in accessing services to ensure that all individuals in the UK and Ireland with hATTR amyloidosis receive consistent, high-quality care.

Between 2020 and 2021, an expert panel from the UK and Ireland convened to discuss proposals for the optimal clinical and genetic management specific to this region, for both patients and pre-symptomatic carriers. The aim of the discussions was to identify the current challenges and provide consensus recommendations. This article does not contain any new studies with human participants or animals performed by any of the authors.

EXPERT PANEL AND CONSENSUS PROCESS

The expert panel comprised 10 amyloidosis specialists, representing the multidisciplinary team, including internal medicine (PNH), renal medicine (JDG), neurology (MMR), clinical genetics (AJG, HC, RM), haematology (MREC) and cardiology (WEM, CJC, RC). Consensus and recommendations evolved during three virtual meetings, held between 29 July 2020 and 8 November 2021 and chaired by Professor Philip Hawkins of the NAC, UK.

Discussions focused on identification of pre-symptomatic TTR variant carriers, diagnostic and pre-symptomatic genetic testing and associated genetic counselling, clinical investigations (for cardiac and neurological disease) and patient access to specialist/multidisciplinary teams and support organizations. Experts shared their current practices, highlighting the process of care and services for the management

of patients across the UK and Ireland. Following each meeting, the discussion was summarized in the form of a draft consensus statement which was shared and refined off-line by the expert panel. Following the third panel meeting, all members agreed and approved the final consensus statements.

Separate recommendations are provided for three distinct subgroups: (1) people with symptoms raising a possibility of hATTR amyloidosis; (2) people with biopsy-confirmed ATTR amyloidosis; and (3) people without symptoms who may have hATTR amyloidosis (i.e. relatives of people with identified TTR variants).

CONSENSUS STATEMENT

People with Symptoms Raising a Possibility of hATTR Amyloidosis

Diagnostic Testing: Steps

The initial steps required for a confirmatory diagnosis of hATTR amyloidosis are determined by clinical signs/symptoms at presentation. The presence of 'red flag' neurological signs and symptoms, characteristic of hATTR amyloidosis, should prompt early genetic testing [9, 20], while patients with cardiac signs/symptoms require further investigation using technetium-99m 3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-DPD) imaging (combined with haematological tests) to exclude light-chain (AL) amyloidosis and confirm ATTR amyloidosis (Fig. 1) [18, 21]. Physicians should be encouraged to arrange diagnostic genetic testing for patients with a positive Tc-DPD imaging scan, to differentiate between hATTR amyloidosis or acquired ATTR wild-type amyloidosis. It is the responsibility of the referring clinician to obtain appropriate consent from the patient for genetic testing [22].

Consensus points: Genetic testing should be considered in anyone suspected to have ATTR amyloidosis, as well as in anyone with a positive Tc-DPD scan. When *TTR* amyloid is suspected, there are two possibilities for testing via a simple blood test: single gene testing (sequencing of the *TTR* gene alone, particularly in cases where there is a strong suspicion of hATTR

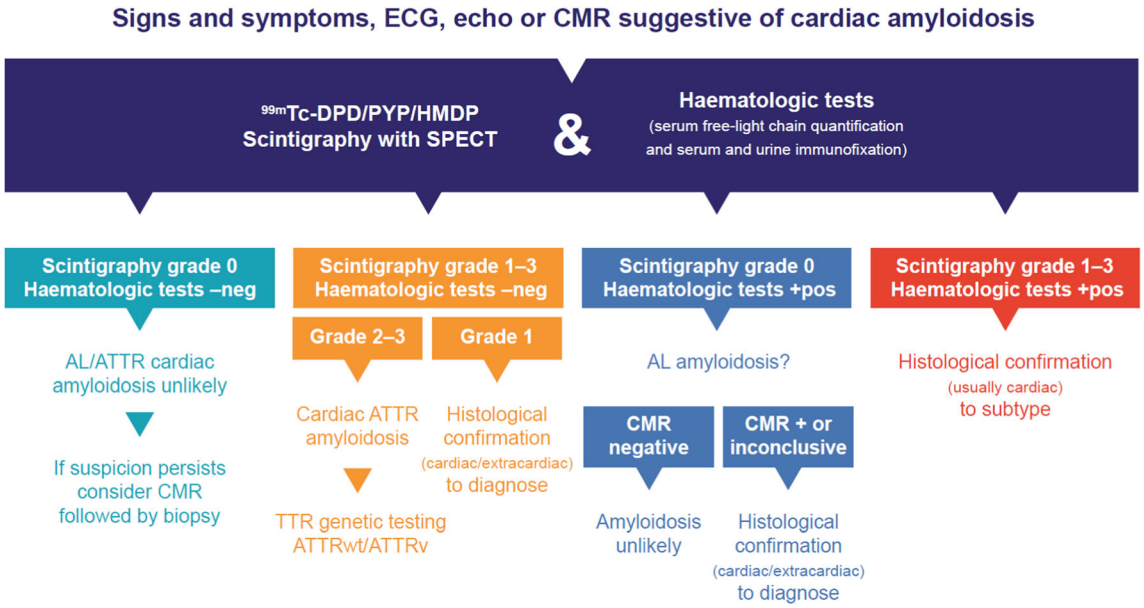

Fig. 1 Diagnostic testing algorithm for cardiac amyloidosis [18]. *^{99m}Tc* technetium-99m, *ATTR* transthyretin amyloidosis, *ATTRv* hereditary transthyretin amyloidosis, *ATTRwt* wild-type transthyretin amyloidosis, *AL* light-chain amyloidosis, *CMR* cardiac magnetic resonance, *DPD* 3,3-diphosphono-1,2-propanodicarboxylic acid, *ECG* electrocardiogram, *HDMP* hydroxymethylene diphosphonate, *PYP* pyrophosphate, *SPECT* single photon emission computed tomography, *TTR* transthyretin

amyloidosis) or panel testing (any cardiomyopathy, neuropathy or amyloidosis panel test that includes *TTR*; the NAC has a hereditary amyloidosis panel that includes the *TTR* gene). The turnaround may be longer for panel testing, so single gene testing is recommended in cases where there is suspicion of hATTR amyloidosis.

Challenges: Access to genetic testing varies across the UK. In England, the National Genomic Testing Directory specifies the testing criteria for hereditary systemic amyloidosis (R204) [23]. In Scotland, Ireland, Northern Ireland and Wales, testing can be accessed by physicians in cases where hATTR amyloidosis is suspected.

Recommendations: Genetic testing should be considered early in the diagnostic work-up of patients suspected of having hATTR amyloidosis. It is the responsibility of the referring clinician to obtain informed consent that is appropriate for the type of test performed on the patient. If a pathogenic variant, likely pathogenic variant or variant of uncertain significance is identified, follow-up should be arranged with Regional Clinical Genetics service to discuss the implications for the family and support cascade testing. Further specialist advice may be sought as required from an amyloidosis centre.

Assessments

For assessment of patients presenting with cardiomyopathy, we recommend the diagnostic algorithm recently proposed by Garcia-Pavia et al. [18] (Fig. 1). For assessment of patients presenting with neuropathy, we propose a new diagnostic algorithm as shown in Fig. 2.

Multidisciplinary Team and Specialist Support

Once a diagnosis is confirmed, it is important to define the level of support and treatment needed from the specialists and multidisciplinary teams for each patient (and their families).

Consensus points: All identified hATTR amyloidosis gene carriers should have access to an amyloidosis specialist or centre.

Recommendations: A baseline consultation with an amyloid disease specialist shortly after genetic diagnosis is recommended for all patients with confirmed hATTR amyloidosis. The purpose of this consultation is to provide context, alleviate patient anxiety, determine next steps for

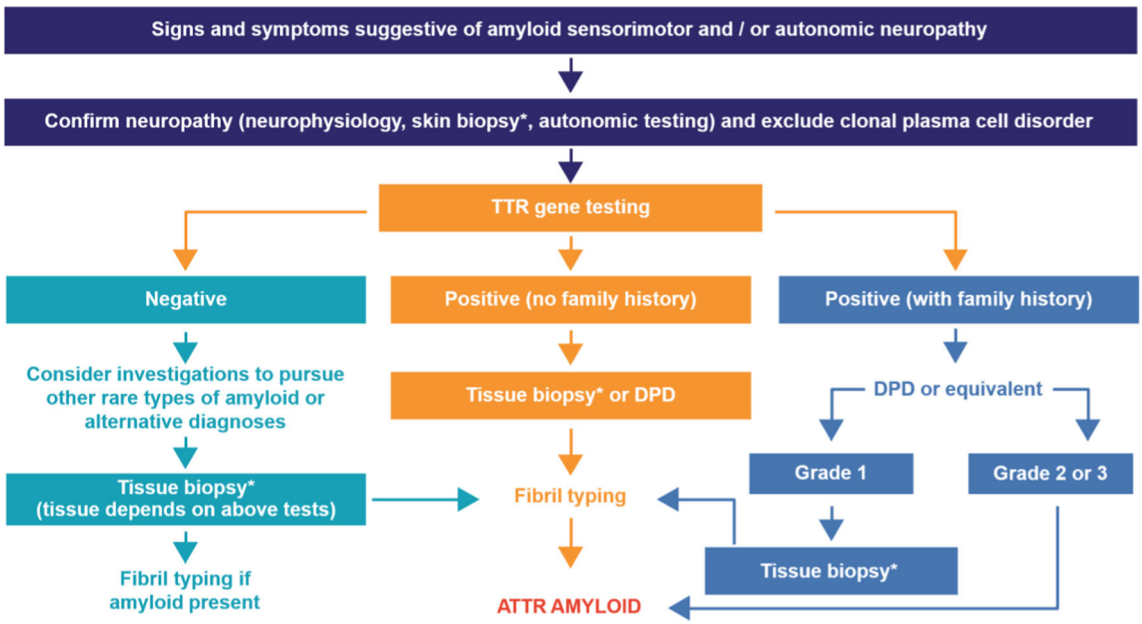

Fig. 2 Diagnostic testing algorithm for neuropathy in patients with symptoms raising a possibility of hATTR amyloidosis *Advice regarding the best location for obtaining biopsy specimens can be obtained from an amyloidosis expert. *ATTR* transthyretin amyloidosis, *DPD* 3,3-diphosphono-1,2-propanodicarboxylic acid imaging, *TTR* transthyretin

management and provide advice on treatment. A date for follow-up should be arranged following this initial baseline consultation.

People with Biopsy-Confirmed ATTR Amyloidosis

Diagnostic Testing: Steps

Consensus points: Genetic testing should be offered to all patients with biopsy-confirmed ATTR amyloidosis to determine whether the patient is affected by the hereditary form or the more common acquired (or wild-type) form of ATTR amyloidosis. Genetic testing should also be offered to all cases of neurological ATTR amyloidosis to identify the causative TTR variant [9]. Testing provides information on the pathogenic TTR genetic variant if present, which can help inform subsequent disease management choices [9]. Genetic testing should generally be organized by the treating physician (often a neurologist or cardiologist, supported where appropriate by geneticists).

Challenges: Ensuring that all treating physicians are aware of the need for genetic testing of patients with ATTR amyloidosis will be a challenge.

Recommendations: Genetic counselling should be recommended to patients at the time of gene testing and follow-up genetic information should be provided for all patients with a confirmed pathogenic *TTR* gene variant [24]. In addition, all first-degree relatives of the proband should be offered the option for referral to genetic services to discuss the options for pre-symptomatic cascade genetic testing [25, 26].

Multidisciplinary Team and Specialist Support

Consensus points: All identified hATTR amyloidosis gene carriers should have access to an amyloidosis specialist or centre.

People Without Symptoms Who May Have hATTR Amyloidosis Variants (i.e. Relatives of People with Identified TTR Variants)

Cascade Genetic Testing and Genetic Counselling

Consensus points: As hATTR amyloidosis is inherited in an autosomal dominant pattern, pre-symptomatic first-degree relatives of a proband may be offered pre-symptomatic genetic testing to determine if they are at risk of developing hATTR amyloidosis [27]. However, pre-symptomatic testing of pre-symptomatic children is not recommended until they are adults and can give informed consent to pre-symptomatic testing [26, 27]. The exact penetrance of each variant is currently unknown and incomplete penetrance is frequent (i.e. not every gene carrier will go on to develop symptoms) [27, 28]. Geneticists, and genetic counsellors in the UK and Ireland, have an important role in counselling each individual prior to pre-symptomatic genetic testing. All clinical geneticists should have prompt access to a cardiologist/neurologist or other physician with experience in treating patients with amyloidosis.

Challenges: If the proband's relative is not symptomatic, genetic testing should be requested by genetics professionals, and these relatives should meet with a genetics professional prior to pre-symptomatic testing.

Recommendations: Genetic counselling should always be recommended before pre-symptomatic testing. Healthcare providers are advised to educate patients on the concept of penetrance as part of the counselling process.

Assessments and Management of Pre-symptomatic Carriers

Recommendations: Cardiac magnetic resonance imaging (MRI) using T1 mapping and extracellular volume quantification, and Tc-DPD imaging, can detect pre-symptomatic cardiac disease [29]. Neurological examination, nerve conduction studies and skin biopsies for epidermal nerve fibre density and amyloid deposits can detect pre-symptomatic neuropathy [20, 27]. Cardiac and neurological assessments should be offered within 10 years of the predicted age of onset relating to the phenotype associated with a particular TTR variant (see predicted age of onset for common variants in Table 1). Specific assessments may include cardiac blood biomarkers, electrocardiogram, echocardiography, Tc-DPD imaging, cardiac MRI, serial neurological clinical assessments, serial nerve conduction studies/electromyography, skin

biopsies for epidermal nerve fibre density and amyloid deposits, and other assessments of autonomic/ocular/gastrointestinal symptoms [20]. Individual tests should be performed at a frequency deemed appropriate by the treating physician.

Challenges: the optimal frequency at which to repeat these investigations is unknown.

Multidisciplinary Team and Specialist Support

Consensus points: All identified *TTR* gene carriers should have access to an amyloidosis specialist and/or centre. Such a network of specialist amyloidosis centres is currently in development in the UK and Ireland.

Recommendations: Prompt consultation with an amyloidosis specialist is recommended for all patients who are found to have a pathogenic *TTR* gene variant. The primary aim of this consultation is to manage potential anxiety and to develop a plan for future monitoring at a frequency determined by the age of onset in the family, or in case of an index case, based on overall average age of onset (see Table 1). Moreover, patient information should be provided at an early stage and patients should be entered into a programme offering continued clinical surveillance. People with pre-symptomatic/potential disease are more likely to present earlier and engage with follow-up and supportive care if treatments are available.

DISCUSSION

This publication is the outcome of an extensive consultation with experts from the UK and Ireland to outline the challenges and recommendations for genetic testing (and diagnosis) of hATTR amyloidosis. Our aim was to provide practical guidance to treating physicians, and emerging amyloid specialist centres, on genetic testing for patients with suspected symptoms of hATTR amyloidosis and biopsy-confirmed ATTR amyloidosis, as well as pre-symptomatic (and symptomatic) family members affected by this disease. We believe that this statement is timely and relevant, as the number of confirmed cases of hATTR amyloidosis continues to grow (and may be much larger than previously recognized), owing to the increasing numbers of people coming forward for cascade genetic testing. The rapid and progressive nature of the disease (and the burden on patients and their families [30]) means that, with effective treatments now available, there is a clear need for timely screening, identification and follow-up of at-risk individuals to initiate treatment at the earliest onset of symptoms. Survival from symptom onset in patients with hATTR amyloidosis ranges from approximately 12 years in patients with the neurological phenotype (such as early-onset V50M) to less than 3 years in patients with cardiac symptoms associated with variants such as T80A and V142I [31]. There is emerging evidence from the NAC, as well as other centres across Europe, that with the advent of Tc-DPD imaging, patients with hATTR amyloidosis are being diagnosed at an earlier disease stage—with associated improved survival time [32].

In addition to the recommendations provided in this statement, we strongly advise treating physicians to encourage their patients with hATTR amyloidosis, as well as pre-symptomatic relatives, to participate in research and to enrol in independent, outcome-based registries run in collaboration with the European Rare Disease Network or the TRANSCEND study. The TRANSCEND study is a prospective, observational study aimed at improving our understanding of the natural history of hATTR amyloidosis and its response to treatment.

More than 130 amyloidogenic TTR variants have been identified worldwide [1, 2]; the most common variants in the UK and Ireland, together with potential 'red flag' signs and predicated age of onset, are listed in Table 1. Penetrance is an important consideration in hATTR amyloidosis, as it may be incomplete depending on the TTR variant. Thus, some variant carriers may remain asymptomatic for life while other TTR variants are associated with very rapid disease progression [33, 34]. In Ireland, T80A (previously known as T60A) is the most common pathogenic variant with a founder population originating from the Donegal region of Ireland, typically giving rise to an hATTR amyloidosis-mixed phenotype [35]. Meanwhile, in the UK, the predominant

disease-causing TTR variants are V142I, T80A and V50M [14, 17].

In conclusion, this consensus statement provides best practice recommendations for the genetic testing and management of people with symptoms raising a possibility of hATTR amyloidosis, patients with biopsy-confirmed ATTR amyloidosis and pre-symptomatic *TTR* gene variant carriers. We believe these recommendations will help increase the identification of affected individuals, help them gain access to regular follow-up and, if needed, treatment to reduce disease progression once they become symptomatic.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

REFERENCES

1. Sekijima Y, Ueda M, Koike H, Misawa S, Ishii T, Ando Y. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: red-flag symptom clusters and treatment algorithm. Orphanet J Rare Dis. 2018;13(1):6. https://doi.org/10.1186/s13023-017-0726-x.

2. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8:31. https://doi.org/10.1186/1750-1172-8-31.

3. Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. Nat Rev Neurol. 2019;15(7):387–404. https://doi.org/10.1038/s41582-019-0210-4.

4. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve. 2007;36(4):411–23. https://doi.org/10.1002/mus.20821.

5. Schmidt HH, Waddington-Cruz M, Botteman MF, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. Muscle Nerve. 2018;57(5):829–37. https://doi.org/10.1002/mus.26034.

6. Conceicao I, Gonzalez-Duarte A, Obici L, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016;21(1):5–9. https://doi.org/10.1111/jns.12153.

7. Arbustini E, Merlini G. Early identification of transthyretin-related hereditary cardiac amyloidosis. JACC Cardiovasc Imaging. 2014;7(5):511–4. https://doi.org/10.1016/j.jcmg.2014.03.007.

8. Sattianayagam PT, Hahn AF, Whelan CJ, et al. Cardiac phenotype and clinical outcome of familial amyloid polyneuropathy associated with transthyretin alanine 60 variant. Eur Heart J. 2012;33(9):1120–7. https://doi.org/10.1093/eurheartj/ehr383.

9. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. J Neurol. 2021;268(6):2109–22. https://doi.org/10.1007/s00415-019-09688-0.

10. Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and treatment of hereditary transthyretin amyloidosis (hATTR) polyneuropathy: current perspectives on improving patient care. Ther Clin Risk Manag. 2020;16:109–23. https://doi.org/10.2147/TCRM.S219979.

11. Lahuerta Pueyo C, Aibar Arregui MA, Gracia Gutierrez A, Bueno Juana E, Menao GS. Estimating the prevalence of allelic variants in the transthyretin gene by analysing large-scale sequencing data. Eur J Hum Genet. 2019;27(5):783–91. https://doi.org/10.1038/s41431-019-0337-1.

12. Rapezzi C, Quarta CC, Obici L, et al. Disease profile and differential diagnosis of hereditary transthyretin-related amyloidosis with exclusively cardiac phenotype: an Italian perspective. Eur Heart J. 2013;34(7):520–8. https://doi.org/10.1093/eurheartj/ehs123.

13. Adams D, Algalarrondo V, Polydefkis M, Sarswat N, Slama MS, Nativi-Nicolau J. Expert opinion on monitoring symptomatic hereditary transthyretin-mediated amyloidosis and assessment of disease progression. Orphanet J Rare Dis. 2021;16(1):411. https://doi.org/10.1186/s13023-021-01960-9.

14. Carr AS, Pelayo-Negro AL, Evans MR, et al. A study of the neuropathy associated with transthyretin amyloidosis (ATTR) in the UK. J Neurol Neurosurg Psychiatry. 2016;87(6):620–7. https://doi.org/10.1136/jnnp-2015-310907.

15. Parker MM, Damrauer SM, Tcheandjieu C, et al. Association of the transthyretin variant V122I with polyneuropathy among individuals of African ancestry. Sci Rep. 2021;11(1):11645. https://doi.org/10.1038/s41598-021-91113-6.

16. Parman Y, Adams D, Obici L, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. 2016;29(Suppl 1):S3–13. https://doi.org/10.1097/wco.0000000000000288.

17. Rowczenio D, Quarta CC, Fontana M, et al. Analysis of the TTR gene in the investigation of amyloidosis: a 25-year single UK center experience. Hum Mutat. 2019;40(1):90–6. https://doi.org/10.1002/humu.23669.

18. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur J Heart Fail. 2021;23(4):512–26. https://doi.org/10.1002/ejhf.2140.

19. Cruz Rodriguez JB, Tallaj JA. Narrative review of pharmacotherapy for transthyretin cardiac amyloid. Ann Transl Med. 2021;9(6):519. https://doi.org/10.21037/atm-20-4636.

20. Conceicao I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations.

Amyloid. 2019;26(1):3–9. https://doi.org/10.1080/13506129.2018.1556156.

21. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation. 2016;133(24):2404–12. https://doi.org/10.1161/circulationaha.116.021612.

22. Royal College of Physicians, Royal College of Pathologists and British Society for Genetic Medicine. Consent and confidentiality in genomic medicine: Guidance on the use of genetic and genomic information in the clinic. 3rd edition. Report of the Joint Committee on Genomics in Medicine. RCP, RCPath and BSGM, London, 2019.

23. National Genomic Test Directory Testing Criteria for Rare and Inherited Disease October 2021. https://www.england.nhs.uk/wp-content/uploads/2018/08/Rare-and-inherited-disease-eligibility-criteria-2021-22-v2.pdf. Accessed 07 Feb 2022.

24. Paneque M, Félix J, Mendes Á, et al. Twenty years of a pre-symptomatic testing protocol for late-onset neurological diseases in Portugal. Acta Med Port. 2019;32(4):295–304. https://doi.org/10.20344/amp.10526.

25. Mendes Á, Metcalfe A, Paneque M, Sousa L, Clarke AJ, Sequeiros J. Communication of information about genetic risks: putting families at the center. Fam Process. 2018;57(3):836–46. https://doi.org/10.1111/famp.12306.

26. Schmidt HH, Barroso F, González-Duarte A, et al. Management of asymptomatic gene carriers of transthyretin familial amyloid polyneuropathy. Muscle Nerve. 2016;54(3):353–60. https://doi.org/10.1002/mus.25210.

27. Obici L, Kuks JB, Buades J, et al. Recommendations for presymptomatic genetic testing and management of individuals at risk for hereditary transthyretin amyloidosis. Curr Opin Neurol. 2016;29(Suppl 1):S27-35. https://doi.org/10.1097/WCO.0000000000000290.

28. Grandis M, Obici L, Luigetti M, et al. Recommendations for pre-symptomatic genetic testing for hereditary transthyretin amyloidosis in the era of effective therapy: a multicenter Italian consensus. Orphanet J Rare Dis. 2020;15(1):348. https://doi.org/10.1186/s13023-020-01633-z.

29. Korthals D, Chatzantonis G, Bietenbeck M, Meier C, Stalling P, Yilmaz A. CMR-based T1-mapping offers superior diagnostic value compared to longitudinal strain-based assessment of relative apical sparing in cardiac amyloidosis. Sci Rep. 2021;11(1):15521. https://doi.org/10.1038/s41598-021-94650-2.

30. Lopes A, Sousa A, Fonseca I, et al. Life paths of patients with transthyretin-related familial amyloid polyneuropathy Val30Met: a descriptive study. J Community Genet. 2018;9(1):93–9. https://doi.org/10.1007/s12687-017-0338-0.

31. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018;39(30):2799–806. https://doi.org/10.1093/eurheartj/ehx589.

32. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. Circulation. 2019;140(1):16–26. https://doi.org/10.1161/circulationaha.118.038169.

33. Sekijima Y. Hereditary transthyretin amyloidosis. 2001 Nov 5 [Updated 2021 Jun 17]. In: Adam MP, Ardinger HH, Pagon RA et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021. https://www.ncbi.nlm.nih.gov/books/NBK1194/. Accessed 07 Feb 2022.

34. Plante-Bordeneuve V, Carayol J, Ferreira A, et al. Genetic study of transthyretin amyloid neuropathies: carrier risks among French and Portuguese families. J Med Genet. 2003;40(11):e120. https://doi.org/10.1136/jmg.40.11.e120.

35. Reilly MM, Staunton H, Harding AE. Familial amyloid polyneuropathy (TTR ala 60) in north west Ireland: a clinical, genetic, and epidemiological study. J Neurol Neurosurg Psychiatry. 1995;59(1):45–9. https://doi.org/10.1136/jnnp.59.1.45.