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When to Suspect and How to Approach a Diagnosis of Amyloidosis

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ABSTRACT

Diagnoses of amyloidosis, particularly transthyretin amyloid cardiomyopathy (ATTR-CM), are steadily increasing throughout the world, but the condition remains underdiagnosed. Patients with amyloidosis may present to a range of medical and surgical specialties, often with multisystemic disease, and a high index of clinical suspicion is required for diagnosis. Bone scintigraphy and cardiovascular magnetic resonance (CMR) imaging offer highly sensitive and specific imaging modalities for cardiac amyloidosis. Histological confirmation of amyloid deposition and amyloid type remains the cornerstone of diagnosis for most amyloid types, with transthyretin amyloid cardiomyopathy the exception, which may be diagnosed by validated nonbiopsy diagnostic criteria in the majority. Histological diagnosis of amyloid has been enhanced by laser capture microdissection and tandem mass spectrometry. Early diagnosis and treatment prior to the development of end-organ damage remains essential to improving morbidity and mortality for patients with amyloidosis.

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KEYWORDS: AL; Amyloid; Amyloidosis; ATTR; Early diagnosis

INTRODUCTION

The amyloidoses are a spectrum of diseases with a common final pathological pathway of protein misfolding, insoluble extracellular fibril formation, disruption of tissue structure, and organ dysfunction. Presentation of systemic amyloidosis is heterogeneous with several organ systems potentially affected. Patients present to a range of medical and surgical specialties and a high index of suspicion is required for diagnosis. Following confirmation of amyloid deposition, determining the amyloid fibril type is crucial to guide treatment and inform prognosis. Treatment of many types of amyloid have improved substantially in recent years, although no treatments to accelerate removal of existing amyloid deposits are currently available, and advanced disease at diagnosis continues to carry a poor prognosis.[1] Reducing diagnostic delay and commencing treatment early is crucial to improving patient outcomes.

PATHOLOGY

The key pathological step in amyloid deposition is protein misfolding and aggregation, which leads to extracellular deposition of amyloid fibrils, disruption of local cellular structure, impaired organ function, and symptomatic amyloidosis. More than 30 "amyloidogenic" proteins have been identified in humans.[2] The propensity for protein misfolding increases in the presence of abnormal protein structure (eg, abnormal fibrinogen Aα-chain protein in hereditary fibrinogen Aα-chain amyloidosis), excessive concentration of a structurally normal protein (eg, serum amyloid A [SAA] protein in systemic [AA] amyloidosis), or for unknown reasons associated with the aging process (eg, transthyretin [TTR] protein in wild-type transthyretin [ATTR] amyloidosis).[2,3] The amyloidogenic protein defines the amyloid type and clinical phenotype and informs diagnosis, treatment, and

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prognosis. Light chain amyloidosis (AL), transthyretin amyloidosis (ATTR), and serum amyloid A amyloidosis (AA) are the most common types of amyloidosis.

AMYLOID TYPES

Features of the most common amyloid types are outlined in Table 1. Clinical phenotype is dictated by the amyloid type, although there remains variability within the same amyloid type; for example, systemic AL can present with cardiac failure due to deposition of amyloid in the myocardium or nephrotic syndrome due to deposition in the kidney, among other presentations. Trends in the diagnosis of amyloidosis have changed significantly in recent years. Systemic AL remains the most commonly diagnosed amyloid type, although there has been a rapid rise in diagnoses of ATTR.[5] This reflects increased awareness, advances in cardiac magnetic resonance (CMR) imaging and bone scintigraphy, and the widespread adoption of validated nonbiopsy diagnostic criteria.[6-8] Conversely, diagnoses of AA have fallen substantially following the widespread use of biologic therapy in the treatment of chronic inflammatory conditions.

CLINICAL SIGNIFICANCE

- Diagnoses of amyloidosis, particularly transthyretin amyloid cardiomyopathy (ATTR-CM), are steadily increasing throughout the world, but the condition remains underdiagnosed.
- Early diagnosis and treatment is essential to improving prognosis and preventing advanced organ dysfunction.
- Bone scintigraphy and cardiac magnetic resonance imaging offer highly sensitive and specific imaging modalities for cardiac amyloidosis.
- ATTR-CM may be diagnosed by validated nonbiopsy diagnostic criteria in the majority of patients.

AL may be localized or systemic. When AL type amyloid deposition is limited to 1 location in the absence of a systemic B-cell clonal disorder, the condition is termed "localized AL." Common sites include the bladder, larynx, tonsil, skin, and lung (pulmonary nodules); treatment is with surgical resection if associated with troublesome symptoms, and prognosis is generally excellent.[9] In systemic AL, an underlying B-cell clonal dyscrasia produces circulating amyloidogenic monoclonal light chains that can deposit as amyloid in almost any tissue. Concomitant multiple myeloma may be confirmed, but often the clonal disorder is subtle and would be otherwise considered a monoclonal gammopathy of unknown significance (MGUS). At diagnosis, cardiac and renal involvement are present in up to 70% and 60% of patients, respectively, whereas liver,

Table 1 Summary of the Fibrillary Precursor Protein, Underlying Cause, Clinical Phenotype, and Treatment of the Most Common Amyloid Types

Amyloid type	Fibrillary precursor protein	Underlying cause	Most common organs involved	Treatment
AL amyloidosis	Monoclonal immunoglobulin light chain	B cell dyscrasia	Kidneys, heart, liver, peripheral NS, autonomic NS, soft tissues, gastrointestinal system	Chemotherapy and / or autologous stem cell transplantation
Wild-type ATTR amyloidosis	Wild-type transthyretin	Unknown, associated with aging	Heart, soft tissues	TTR stabilizer
Hereditary ATTR amyloidosis	Variant transthyretin	*TTR* gene mutation	Heart, peripheral NS, autonomic NS, soft tissues	TTR stabilizers, gene silencing therapy
Systemic AA amyloidosis	Serum amyloid A	Chronic inflammatory conditions	Kidneys, liver, spleen, heart (<1%)	Management of underlying cause of inflammation
LECT2 amyloidosis	LECT2	Unknown	Kidneys, liver	Supportive
Fibrinogen Aα-chain amyloidosis	Variant fibrinogen	Fibrinogen gene mutation	Kidneys, liver	Supportive
AApoA1 amyloidosis	Variant *ApoA1*	*AApoA1* gene mutation	Kidneys, liver, heart	Supportive
Lysozyme	Variant lysozyme	Lysozyme gene mutation	Liver, kidneys, gastrointestinal tract, skin, lacrimal and salivary glands[4]	Supportive
Gelsolin amyloidosis	Variant gelsolin	Gelsolin gene mutation	Peripheral NS, autonomic NS, cranial nerves, kidneys	Supportive

AA = serum amyloid A amyloidosis; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; LECT2 = leucocyte chemotactic factor 2; NS = nervous system.

gastrointestinal, soft tissue, peripheral, and autonomic nerve involvement can also occur.[10]

ATTR occurs when the normal transthyretin tetramer dissociates into amyloidogenic monomers and may be hereditary (hATTR), associated with a *TTR* gene mutation predisposing to protein misfolding, or wild-type (wtATTR), in which an unmutated *TTR* gene produces TTR protein that misfolds for unknown reasons.[11] wtATTR mostly affects elderly males, presenting as a restrictive cardiomyopathy (wtATTR-CM) often with a history of carpal tunnel syndrome or spinal stenosis. hATTR commonly presents with either neuropathy (ATTR-PN), cardiac failure (ATTR-CM), or both (ATTR-mixed) depending, in part, on the specific *TTR* mutation. The p.V142I TTR variant is most commonly associated with a dominant cardiac phenotype, whereas p.T80A is typically associated with a mixed phenotype. The p.V50M TTR variant typically causes ATTR-neuropathy when disease onset is younger than 50 years of age, and ATTR-mixed when older than 50 years.[12] hATTR has an autosomal dominant pattern of inheritance, but disease penetrance is incomplete.

TREATMENT AND THE IMPLICATION OF DIAGNOSTIC DELAYS

The universal aim of treatment in systemic amyloidosis is to reduce ongoing amyloid formation and allow natural amyloid clearance. At present there are no approved treatments to actively accelerate removal of existing amyloid deposits. Therefore, early diagnosis and commencement of therapy before advanced organ dysfunction occurs is essential. However, diagnostic delay remains common.[13–15] Patients have often visited several physicians by the time of diagnosis, and diagnostic delay is associated with more advanced disease at diagnosis.[15,16] Reasons for diagnostic delay are multifactorial and include disease rarity and phenotypic heterogeneity, lack of physician awareness, other disease mimicry, and until recently, a lack of sensitive noninvasive investigations.[17]

PRESENTATION AND RED FLAGS

Patients with amyloidosis present to a range of specialties including cardiology, hematology, nephrology, gastroenterology, neurology, orthopedics, and hand surgery, among others. The likelihood of systemic amyloidosis increases significantly in the presence of multisystemic dysfunction and active inquiry and investigation is required.

Certain populations are at risk of developing amyloidosis and benefit from active monitoring for suggestive signs and symptoms. Patients at risk of systemic AL include those with clonal disorders such as monoclonal gammopathy of uncertain significance, multiple myeloma, Waldenstrom macroglobulinemia, and chronic lymphocytic leukemia. Patients at risk of systemic AA include those with chronic inflammatory conditions such as inflammatory arthropathies, periodic fever syndromes, and inflammatory bowel disease, and either recurrent or chronic infections such as bronchiectasis and tuberculosis. Routine inquiry for symptoms and assessment of renal function, urine dipstick, liver function, and NT-proBNP improve the likelihood of diagnosing amyloidosis early. Patients with a family history of hATTR may be offered predictive genetic testing, and carriers should undergo age-appropriate work up depending on the amyloid type.[18]

Cardiac amyloidosis is most commonly AL or ATTR type and typically presents with symptoms of heart failure or conduction abnormalities. Red flags for cardiac AL include rapid onset heart failure symptoms, systemic symptoms such as weight loss and fatigue, other organ system involvement, and presence of a clonal disorder. ATTR-CM typically has a more indolent heart failure presentation than cardiac AL but should be considered in elderly Caucasian males or individuals of African ancestry particularly when there is a history of carpal tunnel syndrome, spinal stenosis, or tendon rupture. The most common hATTR-CM is associated with the p.V142I TTR variant, which affects individuals of African ancestry; the population prevalence of this particular variant is nearly 4%, although disease penetrance appears to be low. Other red flags for hATTR include peripheral or autonomic neuropathy, a family history of cardiac disease or neuropathy, and Irish (p.T80A), Portuguese, Japanese, or Swedish (all p.V50M) ancestry.

Renal amyloidosis presents with proteinuria and or chronic kidney disease depending on the location of amyloid deposits within the kidney. New onset proteinuria in high-risk groups is a red flag for the development of amyloidosis.

Soft tissue amyloid deposition gives rise to nail dystrophy, easy bruising, carpal tunnel syndrome, macroglossia, shoulder infiltration, and periorbital bruising. Both macroglossia and periorbital purpura are pathognomonic of systemic AL. Carpal tunnel syndrome occurs in both AL and ATTR, and in ATTR especially may predate diagnosis by many years.[19] Flexor retinaculum histology obtained at carpal tunnel decompression surgery may demonstrate amyloid deposition.

Peripheral neuropathy is present in up to 15% of patients with AL at diagnosis and is often the presenting feature in neuropathic forms of hATTR (eg, associated with p.V50M and p.T80A variants).[20]

Visceral organ amyloidosis presents with nonspecific symptoms such as fatigue, weight loss, anorexia, and abdominal fullness; rarely, advanced liver amyloidosis can cause jaundice.

APPROACH TO DIAGNOSIS

The diagnosis of systemic amyloidosis requires a stepwise approach starting with a high index of suspicion.[3] A comprehensive history is crucial to identify extent of organ involvement and relevant underlying conditions. This is followed by basic investigations (Table 2) to support the initial clinical suspicion and assess organ function. Subsequent histological demonstration of amyloid deposits and the

Table 2 Noninvasive Investigation Options for Systemic Amyloidosis

System	Investigation	Suggestive findings
Cardiac	Cardiac biomarkers	Persistently elevated serum NT-proBNP and troponin
	ECG	Heart block, atrial arrhythmia, small QRS complexes, poor R wave progression, pseudoinfarction pattern
	Echocardiogram	Biventricular hypertrophy, small left ventricular cavity, reduced global longitudinal strain with apical sparing, pericardial effusion, diastolic dysfunction
	DPD scintigraphy	Cardiac uptake >99% sensitive for ATTR-CM also present in ~30% of cardiac AL amyloidosis[21]
	CMR	Elevated T1, increased extracellular volume, late gadolinium enhancement in a subendocardial, diffuse, or transmural pattern[22-24]
Renal	Creatinine and eGFR	Frequently abnormal but may be normal
	Urinary proteinuria	Nephrotic range common in AL and AA amyloidosis. Often minimal in ALECT2 and hereditary amyloidoses. Not a feature of wtATTR amyloidosis.
Peripheral NS	Nerve conduction studies	Small fiber neuropathy in early disease, progressing to a large fiber axonal sensorimotor lower limb predominant neuropathy[20]. Carpal tunnel syndrome, especially in ATTR
Autonomic NS	Postural blood pressure	Postural blood pressure drop, especially in AL and hATTR
Liver	Liver function tests	Raised GGT and alkaline phosphatase. Raised bilirubin in advanced disease
	Ultrasound abdomen	Hepatomegaly and or splenomegaly
Special	SAP scintigraphy	Identifies amyloid deposits in the liver, spleen, kidneys, adrenal glands and bones[25]. Does not provide information on the gastrointestinal tract, NS, or myocardium
	Genotyping	Consider in all cases of ATTR amyloidosis and in the presence of a suggestive family history

AA = serum amyloid A amyloidosis; AL = light chain amyloidosis; ATTR = transthyretin amyloidosis; ATTR-CM = transthyretin amyloid cardiomyopathy; CMR = cardiac magnetic resonance imaging; DPD = 99mTechnetium labeled 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GGT - gamma-glutamyl transferase; hATTR = hereditary ATTR; NS = nervous system; SAP = 123Iodine-labeled serum amyloid P scintigraphy; wtATTR = wild type ATTR.

amyloid fibril protein are usually required to confirm the diagnosis, followed by investigations to identify underlying causes. ATTR-CM is the exception to the requirement for histological confirmation because the diagnosis can often be made using a validated nonbiopsy diagnostic algorithm (discussed below).[5]

CARDIAC INVESTIGATIONS

Serial serum NT-proBNP may be used to screen for the development of cardiac amyloidosis in at-risk groups, although they can be normal in early disease. Echocardiography offers a widely available noninvasive tool to screen for features of cardiac amyloidosis such as left ventricular hypertrophy of >12mm[26] (Figure A); ventricular hypertrophy alone is of limited sensitivity and specificity, although suspicion increases in the absence of an alternative cause, and with concomitant small or normal QRS voltages on the electrocardiogram. More advanced echocardiographic measures such as global longitudinal strain offer greater specificity for diagnosing cardiac amyloidosis although are not widely acquired and are further limited by significant interoperator variability (Figures B and C). Cardiac uptake by ^{99m}Technetium labeled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD; Figures E and F) or pyrophosphate (PYP) scintigraphy is >99% sensitive for cardiac ATTR amyloid deposition but only 86% specific due to cardiac uptake in a proportion of patients with cardiac AL.[5] Gadolinium-enhanced CMR is unique in allowing the characterization of myocardial tissue and is highly sensitive and specific for cardiac amyloidosis. Characteristic findings including raised native T1 signal, increased extracellular volume, and late gadolinium enhancement (Figures G, H, and I, respectively).[27] Cardiac AL and ATTR-CM cannot be distinguished by CMR or DPD scintigraphy alone, and further workup is essential to avoid incorrect diagnosis and allow early commencement of appropriate treatment.

INVESTIGATIONS OF UNDERLYING DISORDER

Early assessment for a clonal disorder is essential to identify patients with systemic AL who may benefit from urgent chemotherapy. The combination of serum free light chain assay and serum and urine protein electrophoresis with immunofixation will identify the underlying clonal disease in up to 99% of patients with systemic AL;[28] however, it is important to note that there may be an incidental clonal disease in association with ATTR-CM such that identification of amyloid and a clonal disease alone are insufficient to confirm a diagnosis of AL.

If AA is diagnosed on the basis of histology, focused history and investigations are required to identify the underlying cause of chronic inflammation, a necessary prerequisite for the diagnosis. Serial measurement of the acute phase protein SAA (or C-reactive protein as a surrogate) is required to determine the degree of ongoing inflammation and is used to monitor response to anti-inflammatory treatment. Outcome in AA is directly related to SAA concentration with sustained suppression of SAA after diagnosis to below <3 mg/L conferring the most favorable prognosis.

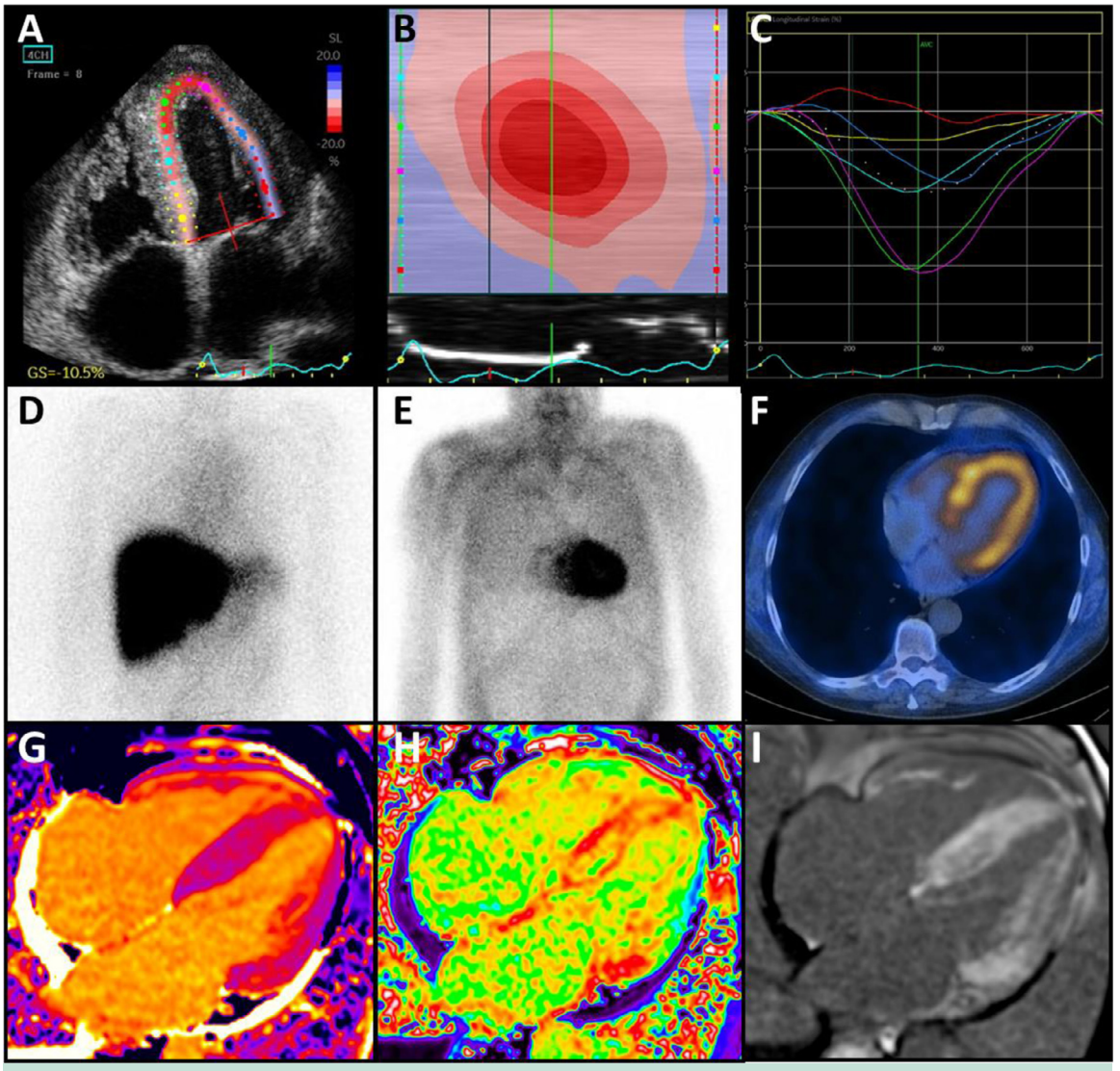

Figure Imaging features of systemic amyloidosis. Echocardiography: **(A)** 4-chamber view with biventricular hypertrophy, and **(B** and **C)** "bullseye" pattern of apical sparing of longitudinal strain and reduced global longitudinal strain. Nuclear medicine imaging: **(D)** SAP scintigraphy demonstrating liver amyloid deposition, **(E)** DPD scintigraphy with Perugini grade 3 cardiac uptake, **(F)** single-photon emission computer tomography (SPECT) demonstrating biventricular cardiac uptake. Cardiac magnetic resonance imaging: **(G)** diffusely elevated T1 values at 1149 ms, **(H)** diffusely elevated extracellular volume of 63%, and **(I)** diffuse transmural late gadolinium enhancement. DPD = 3,3-diphosphono-1,2-propanodicarboxylic acid; SAP = serum amyloid P.

NONBIOPSY DIAGNOSIS OF ATTR-CM

A diagnosis of ATTR-CM can be made without histology if all of the following validated nonbiopsy diagnostic criteria are met: heart failure, a suggestive or characteristic amyloid echocardiogram or CMR, a Perugini grade 2 or 3 DPD/PYP scan, a normal serum free light chain ratio, absence of a serum paraprotein by electrophoresis and immunofixation, and absence of urinary Bence Jones protein by urine immunofixation.[5] Diagnosis of ATTR-CM should be followed by sequencing of the *TTR* gene to distinguish between hATTR-CM and wtATTR-CM. A negative plasma cell dyscrasia workup using all 3 of the tests listed is essential to exclude cardiac AL, which is associated with cardiac uptake on DPD scintigraphy in approximately 30% of patients and a Perugini grade 2 or 3 DPD scan in up to 10% of cases.[21]

AMYLOID CONFIRMATION AND TYPING

Histological identification and typing of amyloid deposits in an affected organ is the gold standard for amyloidosis. When a target organ biopsy is deemed high risk, screening biopsies such as a fat aspirate, bone marrow trephine, or gastrointestinal biopsy may identify amyloid with varying sensitivities.[29] Amyloid appears as an acellular, eosinophilic

material on light microscopy, with randomly orientated nonbranching fibrils of approximately 10 nm in diameter on electron microscopy.[3] Amyloid deposition is confirmed by observing apple green birefringence following Congo red staining when viewed under cross polarized light. Amyloid type may be determined by immunohistochemical staining using a panel of antibodies, although sensitivity is limited with up to 30% cases showing no immune-specific staining.[30] Laser capture microdissection and tandem mass spectrometry of amyloidotic tissue is able to identify presence and type of amyloid in >95% of cases including >80% of those in which immunohistochemistry is indeterminate and requires only a small quantity of amyloidotic tissue.[30,31]

SUMMARY

Diagnoses of amyloidosis, particularly ATTR-CM, are steadily increasing throughout the world, but the condition remains underdiagnosed. Bone scintigraphy and CMR offer highly sensitive and specific imaging modalities for cardiac amyloidosis, and a validated nonbiopsy diagnostic algorithm enables diagnosis in the absence of histology in a majority of patients with ATTR-CM. Histological diagnosis of amyloid has been enhanced by laser capture microdissection and tandem mass spectrometry. Early diagnosis prior to the development of end-organ damage remains crucial to improving morbidity and mortality for patients with amyloidosis.

CME STATEMENT

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References

1. Wechalekar AD, Schonland SO, Kastritis E, et al. A European collaborative study of treatment outcomes in 346 patients with cardiac stage III AL amyloidosis. *Blood* 2013;121(17):3420–7.
2. Sipe JD, Benson MD, Buxbaum JN, et al. Nomenclature 2014: amyloid fibril proteins and clinical classification of the amyloidosis. *Amyloid* 2014;21(4):221–4.
3. Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet* 2016;387(10038):2641–54.
4. Sattianayagam PT, Gibbs SDJ, Rowczenio D, et al. Hereditary lysozyme amyloidosis – phenotypic heterogeneity and the role of solid organ transplantation. *J InternMed* 2012;272(1):36–44.
5. Ravichandran S, Lachmann HJ, Wechalekar AD. Epidemiologic and survival trends in amyloidosis, 1987–2019. *N Engl J Med* 2020;382(16):1567–8.
6. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation* 2016;133(24):2404–12.
7. Maceira AM, Joshi J, Prasad SK, et al. Cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 2005;111(2):186–93.
8. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mtc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. *J Am Coll Cardiol* 2005;46(6):1076–84.
9. Mahmood S, Bridoux F, Venner CP, et al. Natural history and outcomes in localised immunoglobulin light-chain amyloidosis: a long-term observational study. *Lancet Haematol* 2015;2(6):e241–50.
10. Vaxman I, Gertz M. Recent advances in the diagnosis, risk stratification, and management of systemic light-chain amyloidosis. *Acta Haematologica* 2019;141(2):93–106.
11. Colon W, Kelly JW. Partial denaturation of transthyretin is sufficient for amyloid fibril formation in vitro. *Biochemistry* 1992;31(36):8654–60.
12. Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy. *J Neurol* 2021;268:2109–22.
13. Lousada I, Comenzo RL, Landau H, Guthrie S, Merlini G. Light chain amyloidosis: patient experience survey from the Amyloidosis Research Consortium. *Adv Ther* 2015;32(10):920–8.
14. Ladefoged B, Dybro A, Povlsen JA, Vase H, Clemmensen TS, Poulsen SH. Diagnostic delay in wild type transthyretin cardiac amyloidosis - A clinical challenge. *Int J Cardiol* 2020;304:138–43.
15. Lane T. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation* 2019;140:16–26.
16. Bishop E, Brown EE, Fajardo J, Barouch LA, Judge DP, Halushka MK. Seven factors predict a delayed diagnosis of cardiac amyloidosis. *Amyloid* 2018;25(3):174–9.
17. Mircsof D. Diagnosis of amyloidosis: a survey of current awareness and clinical challenges among cardiologists in Switzerland. *Cardiol Ther* 2020;9(1):127–38.
18. Conceição 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.
19. Milandri A, Farioli A, Gagliardi C, et al. Carpal tunnel syndrome in cardiac amyloidosis: implications for early diagnosis and prognostic role across the spectrum of aetiologies. *Eur J Heart Fail* 2020;22(3):507–15.
20. Kapoor M, Rossor AM, Jaunmuktane Z, Lunn MPT, Reilly MM. Diagnosis of amyloid neuropathy. *Pract Neurol* 2019;19(3):250–8.
21. Rapezzi C, Quarta CC, Guidalotti PL, et al. Usefulness and limitations of 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in the aetiological diagnosis of amyloidotic cardiomyopathy. *Eur J Nucl Med Mol Imaging* 2011;38(3):470–8.
22. Fontana M, Banypersad SM, Treibel TA, et al. Native T1 mapping in transthyretin amyloidosis. *JACC Cardiovasc Imaging* 2014;7(2):157–65.
23. Fontana M, Pica S, Reant P, et al. Prognostic value of late gadolinium enhancement cardiovascular magnetic resonance in cardiac amyloidosis. *Circulation* 2015;132(16):1570–9.
24. Martinez-Naharro A, Kotecha T, Norrington K, et al. Native T1 and extracellular volume in transthyretin amyloidosis. *JACC Cardiovasc Imaging* 2019;12(5):810–9.
25. Hawkins PN, Lavender JP, Pepys MB. Evaluation of systemic amyloidosis by scintigraphy with 123i-labeled serum amyloid p component. *N Engl J Med* 1990;323(8):508–13.
26. Gillmore JD, Wechalekar A, Bird J, et al. Guidelines on the diagnosis and investigation of AL amyloidosis. *Br J Haemtol* 2015;168(2):207–18.
27. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail* 2019;12(9):e006075.

28. Palladini G, Russo P, Bosoni T, et al. Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. *Clin Chem* 2009;55(3):499–504.
29. Cohen OC, Sharpley F, Gilbertson JA, et al. The value of screening biopsies in light-chain (AL) and transthyretin (ATTR) amyloidosis. *Eur J Haemtol* 2020;105(3):352–6.
30. Rezk T, Gilbertson JA, Mangione PP, et al. The complementary role of histology and proteomics for diagnosis and typing of systemic amyloidosis. *J Pathol Clin Res* 2019;5(3):145–53.
31. Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood* 2009;114(24):4957–9.