Original Article

Diagnosis and referral of patients with AL amyloidosis in Portugal: results from a Delphi panel

Rui Bergantim[a,b,c,d],*, André Caetano[e], Francisco F. Silva[f], Isabel Tavares[a,b,g], Manuela Ferreira[h], Ana R. Jaime[i], Graça V. Esteves[h]

Abstract Light chain amyloidosis (AL) is a complex disorder defined by the extracellular deposition of insoluble amyloid fibrils formed by intact or fragmented immunoglobulin light chains, leading to cell dysfunction, rapid organ deterioration, and, ultimately, death. Although the clinical presentation of AL is directly connected to organ involvement, signs and symptoms of AL are frequently nonspecific, misinterpreted, and late recognized. Thus, an early diagnosis combined with effective therapies to cease disease progression and rescue organ function is essential. The aim of this study was to assess the knowledge and characterize the current clinical practice regarding AL diagnosis and referral among Portuguese physicians. A Delphi-like panel (one round only) with a group of national experts from different medical specialties (cardiology, hematology, internal medicine, nephrology, and neurology) was carried out online, in which 30 statements were classified using a 4-point Likert scale. For each statement, the consensus level was set at 70% for "fully agree/disagree" and the majority level was defined as >70% in agreement or disagreement. Although the results suggest the existence of adequate general knowledge of AL amyloidosis, they also disclosed the necessity to raise awareness for this disease. Overall, this Delphi panel revealed a high lack of consensus regarding the diagnosis and early management of patients with AL among different specialties despite the qualified majority obtained in 26 statements. An optimized strategy for AL early diagnosis, transversal to several medical fields, is urgently needed. Moreover, referral centers with access to diagnostic technology and a network of diverse specialties should be established to foster an early diagnosis and better disease approach to boost the possibility of a better outcome for patients with AL.

Keywords: amyloid, diagnosis, immunoglobulin light chain, nephropathy, Delphi panel

Introduction

Light chain amyloidosis (AL amyloidosis) is a complex and challenging disorder characterized by extracellular accumulation of insoluble amyloid fibrils composed of intact or fragmented immunoglobulin light chains.[1,2] It is commonly associated with classic plasma cell dyscrasias, such as monoclonal gammopathy of unknown significance (MGUS), smoldering myeloma, multiple myeloma, and, less frequently, Waldenstrom macroglobulinemia and lymphoplasmacytic and marginal lymphoma. AL amyloidosis is the most diagnosed form of systemic amyloidosis, with an estimated incidence of approximately 1 per 100,000 persons/year.[3] The accumulation of monoclonal light chains kappa (κ), lambda (λ), or preceding intermediates induces proteotoxicity, leading to cell dysfunction, rapid organ deterioration, and, ultimately, death.[4-6] Therefore, an early diagnosis combined with effective therapies to cease disease progression and rescue organ function is essential.[7,8]

Although the clinical presentation of AL amyloidosis is directly related to organ involvement, signs and symptoms of AL are usually nonspecific, misinterpreted, and late recognized. Overall, AL amyloidosis should be suspected in a clinical scenario characterized by nephrotic range proteinuria, heart failure with preserved ejection fraction, nondiabetic peripheral neuropathy, unexplained hepatomegaly, or subacute to chronic diarrhea.[1] Nonetheless, these clinical manifestations are not specific to AL amyloidosis and overlap with other types of amyloidoses and disorders.[9] Moreover, a lack of familiarity with the diagnosis might also occur,[10] eventually leading to a late or underdiagnosis. Accordingly, up to 20% of patients with AL amyloidosis have been incorrectly diagnosed,[9] and 37% have their diagnosis delayed in more than a year because 4 of 10 patients have to consult five different physicians before receiving a definite AL amyloidosis diagnosis.[11] In 44% of patients, the diagnosis is only made on disease progression to stages IIIa and IIIb, leading to a median overall survival of 14 and 5 months, respectively.[12,13] This induces near-irreversible loss of vital organ function, a worse prognosis, and a high premature mortality rate.[8]

Therefore, it is mandatory to anticipate organ loss and promote the rescue of its vital function by fostering an earlier and faster diagnosis and treatment. Overall, establishing a definite diagnosis of AL amyloidosis involves a series of events, as shown in Fig. 1.

[a] Faculty of Medicine of the University of Porto (FMUP), Porto, Portugal, [b] i3S - Institute for Research and Innovation in Health, University of Porto, Porto, Portugal, [c] Cancer Drug Resistance Group, Institute of Molecular Pathology and Immunology of the University of Porto (IPATIMUP), Porto, Portugal, [d] Department of Hematology, Centro Hospitalar Universitário de São João, Porto, Portugal, [e] Hospital de Egas Moniz, Centro Hospitalar de Lisboa Ocidental, Lisbon, Portugal, [f] Hospital da Cruz Vermelha, Lisbon, Portugal, [g] Nephrology Service, Centro Hospitalar e Universitário de São João, Porto, Portugal, [h] Hospital de Santa Maria, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal, [i] Medical Department—Hematology, Janssen-Cilag, S.A., Lisbon, Portugal

*Corresponding author. Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. E-mail address: rui.bergantim@gmail.com (Rui Bergantim).

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On AL amyloidosis suspicion, through analysis of specific signs or symptoms, organ involvement, and the presence of a monoclonal component, the differential diagnosis should begin with an abdominal fat aspirate analysis or a biopsy of the most affected organ to investigate the presence of amyloid deposits in suspected organs or peripheral tissues.[14] The detection of amyloid deposits starts with Congo red staining.[4,14] The next step of the diagnosis is amyloid typing, mainly through immunohistochemistry. In some cases, more than one type of amyloid can be identified. In clinical practice, this is usually accomplished by direct immunofluorescence on frozen tissues or immunohistochemistry on fixed samples.[4] Mass spectrometry is the gold standard for amyloid typing, mainly in cases with inconclusive or equivocal immunohistochemistry results; however, this technique is unavailable in most centers. Thus, including biomarkers, such as NT-proBNP, albuminuria, and serum alkaline phosphatase (ALP), in the surveillance of patients with high-risk MGUS contributes to an early diagnosis of AL amyloidosis, even before the establishment of organ damage.

The primary purpose of the current treatment of AL amyloidosis was to decrease the amyloidogenic-involved light chains without causing significant damage.[15] Hence, early identification of signs and symptoms, accompanied by an accurate diagnosis, fostering the proper management of patients with AL, is urgently needed. Thus, a Delphi panel was organized with experts from different medical specialties to assess the knowledge and characterize the current clinical practice regarding AL amyloidosis diagnosis and referral among Portuguese physicians.

Methods

This study assessed the agreement level of several Portuguese physicians regarding signs and symptoms, complementary diagnostic examinations, diagnosis, and patient referral for AL amyloidosis.

A group of six experts in AL amyloidosis with different medical specialties—cardiology (n = 1), hematology (n = 2), internal medicine (n = 1), nephrology (n = 1), and neurology (n = 1)—with a vast knowledge of this clinical condition acquired through clinical practice and global engagement arising from the research conducted in the framework of the PhD on the subject was assembled in a Focus Group. The Focus Group defined 30 statements related to suspicion, diagnosis, and referral of patients with AL amyloidosis. The statements were divided into five main areas: (I) Overall, (II) Signs and Symptoms, (III) Complementary Diagnostic Exams, (IV) Diagnosis, and (V) Patients Referral (Table 1). An external private source moderated the Focus Group meeting. All the validations were conducted by the experts from the Focus Group and the team that moderated the process. After quality testing by all the members involved, the final questionnaire was uploaded to an online platform to execute a Delphi-like panel (DP) of only one round (Fig. 2).

A diverse group of national health professionals, including cardiologists, hematologists, general practitioners, internists, nephrologists, and neurologists, were invited by their respective national specialty societies and/or by the external vendor to voluntarily participate by responding anonymously to the questionnaire. Specifically, the panelists were asked to categorize the previously defined 30 statements in a randomized order using a 4-point Likert scale: "fully disagree," "disagree," "agree," and "fully agree." The consensus agreement level was set according to the definitions in Fig. 2. In brief, for each statement, the consensus level was set at 70% for "fully agree" or "fully disagree," and the majority level was defined as >70% in agreement ("fully agree" plus "agree") or disagreement ("fully disagree" plus "disagree"). The responses were analyzed by the frequency distribution through the presented 4-point Likert scale.

Results

This one-round Delphi-like panel included 108 physicians: 36 (33.4%) hematologists, 32 (29.6%) nephrologists, 17 (15.7%) general practitioners, 10 (9.3%) internists, 7 (6.5%) cardiologists, and 6 (5.5%) neurologists. Physicians were requested to categorize the 30 statements elaborated by the Focus Group using a 4-point Likert scale (Table 1 and Supplementary Table 1, http://links.lww.com/PBJ/A33).

The results of the questionnaire showed that only the following three statements were categorized as consensus, reaching a 70% "fully agree" response rate, precisely: (1) *If a sign, symptom, or complementary diagnosis makes me suspect AL amyloidosis, I should investigate it*; (2) *Diagnostic suspicion is essential. Poor prognosis is directly related to the elapsed time between the onset of symptoms and the start of specific treatment*; and (6) *If*
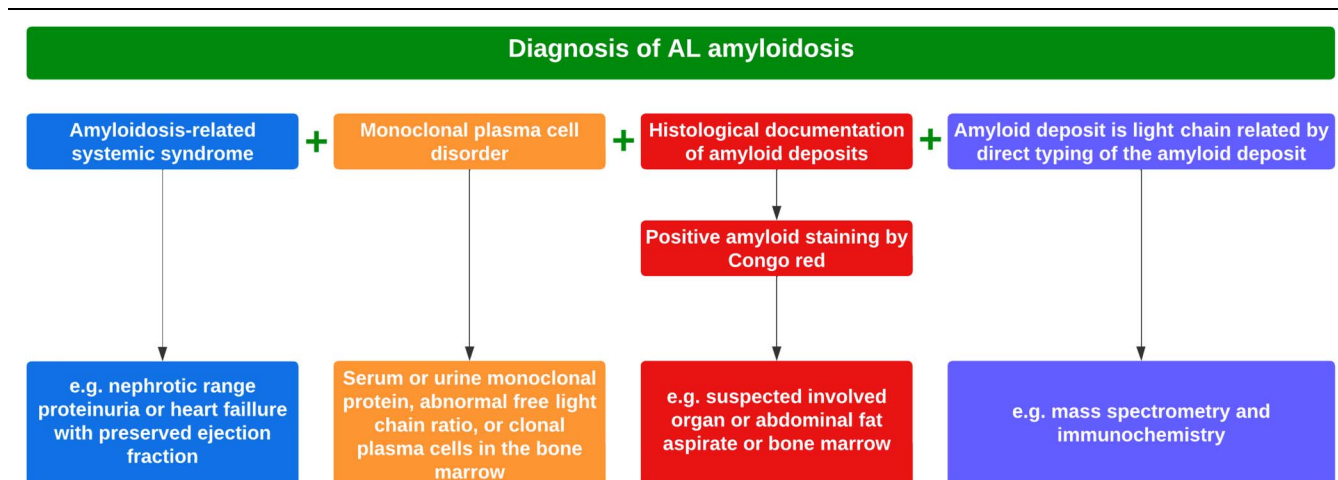

Figure 1. Requirements for establishing AL amyloidosis diagnosis.[41,42]

Table 1.

Defined statements for the Delphi-like panel.

I. Overall
(1)	If a sign, symptom, or diagnostic test makes me suspect AL amyloidosis, I should look for it.
(2)	Diagnostic suspicion is essential. Poor prognosis is directly related to the elapsed time between the onset of symptoms and the initiation of specific treatment.
(3)	Clinical presentation is insufficient to establish the differential diagnosis between AL amyloidosis and other types of amyloidosis.
(4)	Monoclonal gammopathy of undetermined significance (MGUS), Multiple Myeloma, and Waldenström's Macroglobulinemia are AL amyloidosis' most frequent precursor diseases.
(5)	Symptoms of AL amyloidosis are primarily non-specific and are recognized late, and the damage to the organ involved is usually irreversible.
(6)	If symptoms suggestive of systemic amyloidosis appear in a patient with no known history of monoclonal gammopathy, the patient should be screened as early as possible.
(7)	Constitutional symptoms (fatigue, asthenia, weakness, weight loss), dyspnea, unexplained diarrhea, and foamy urine in patients over 50 years make me suspect AL amyloidosis.

II. Signs and Symptoms
(8)	In patients with albuminuria and cardiac dysfunction (left ventricular hypertrophy with "infiltrative" shiny appearance and interatrial septal thickening) associated with electrocardiogram with low-voltage complexes, I always suspect AL amyloidosis.
(9)	AL amyloidosis should be considered in patients with monoclonal gammopathy who present changes in cardiac (NT-proBNP/TNT) or urinary (albuminuria) markers during their follow-up.
(10)	Macroglossia and periorbital ecchymosis are specific signs of AL amyloidosis, even though they are less frequent.
(11)	Carpal tunnel syndrome, hepatomegaly, and hypotension should raise suspicion for the diagnosis of AL amyloidosis.
(12)	Heart failure and nephrotic syndrome should raise the suspicion of AL amyloidosis.
(13)	AL amyloidosis should be considered in a patient with a picture suggestive of polyneuropathy and autonomic dysfunction.
(14)	When I suspect AL amyloidosis with cardiac involvement, I should order NT-proBNP, troponin, echocardiogram/Doppler, and myocardial strain. When an echocardiogram/Doppler is not diagnostic for poor imaging, I consider cardiac MRI.

III. Complementary Diagnostic Exams
(15)	When I suspect AL amyloidosis with renal involvement, I should order serum albumin and creatinine and quantify albuminuria/proteinuria.
(16)	When I suspect AL amyloidosis with liver involvement, I should measure alkaline phosphatase levels and perform a liver ultrasound.
(17)	Tests of greater diagnostic specificity are serum and urinary protein immunofixation and free light chain assay.
(18)	Abdominal fat biopsy should be performed with a request for amyloid protein detection and characterization.
(19)	In diagnosing AL amyloidosis, Congo Red staining should be applied to the biopsy specimen.
(20)	Congo Red identification of amyloid deposits in abdominal fat biopsy is insufficient for diagnosing AL amyloidosis, even in monoclonal gammopathy.
(21)	Typing of amyloid deposits with immunohistochemistry for light chains is mandatory to confirm AL amyloidosis.
(22)	When immunohistochemistry is inconclusive, mass spectrometry is recommended to confirm AL amyloidosis.
(23)	If AL amyloidosis is suspected and abdominal fat biopsy is insufficient, a biopsy of the involved organ is recommended.
(24)	Bone biopsy with identification of vascular amyloid deposition associated with monoclonal gammopathy in a patient with cardiac and renal symptoms allows the assumption of AL amyloidosis diagnosis.

IV. Diagnosis
(25)	MGUS is insufficient to diagnose AL amyloidosis in patients with cardiac amyloidosis since about 1/3 of patients with transthyretin amyloidosis (ATTR) may have MGUS.
(26)	In patients with cardiac amyloidosis, technetium-99m (99mTC) scintigraphy helps to decide the differential diagnosis between AL amyloidosis and ATTR amyloidosis.
(27)	When AL amyloidosis is suspected, bone biopsy and myelogram are essential for plasma cell quantification and exclusion of other hematologic diseases.

V. Patient Referral
(28)	In case of AL amyloidosis suspicion, the patient should be referred to the Hemato-Oncology consultation and the medical field related to the organ/organs affected (Nephrology, Neurology, Cardiology, Gastroenterology).
(29)	Timely referral of AL amyloidosis patients to Hemato-Oncology allows for faster diagnosis.
(30)	A faster diagnosis allows treatment to be initiated at an earlier stage of the disease, contributing to disease stabilization and, in some cases, reversing the clinical course of the affected organ, with improved quality of life and patient survival.

symptoms suggestive of systemic amyloidosis appear in a patient with no known history of monoclonal gammopathy, it should be screened as early as possible. The remaining statements (except for statement 20) obtained a qualified majority, expressly, more than 70% of the collective agreement ("fully agree" and "agree") (Fig. 3).

Regarding the "overall statements" about AL amyloidosis, higher rates of disagreement were obtained in the following statements: (4) *Monoclonal gammopathy of undetermined significance (MGUS), Multiple Myeloma, and Waldenström's Macroglobulinemia are AL amyloidosis' most frequent precursor diseases* and (7) *Constitutional symptoms (fatigue, asthenia, weakness, weight loss), dyspnoea, unexplained diarrhea, and foamy urine in patients over 50 years make me suspect of AL amyloidosis.*

Concerning the statements about "signs and symptoms," the rate of combined discordance varied between 0.93% and 15.74%, particularly relating to (8) *In patients with albuminuria and cardiac dysfunction (left ventricular hypertrophy with "infiltrative" shiny appearance and interatrial septal thickening) associated with electrocardiogram with low-voltage complexes, I always suspect of AL amyloidosis;* (10) *Macroglossia and periorbital ecchymosis are specific signs of AL amyloidosis, even though they are less frequent;* and (11) *Carpal tunnel syndrome, hepatomegaly, and hypotension should raise suspicion for the diagnosis of AL amyloidosis* (Fig. 3).

The lowest level of agreement was obtained in "complementary diagnosis exams" and "diagnosis." In 7 of 13 statements, the percentage of "fully disagree" and "disagree" varied between 8%
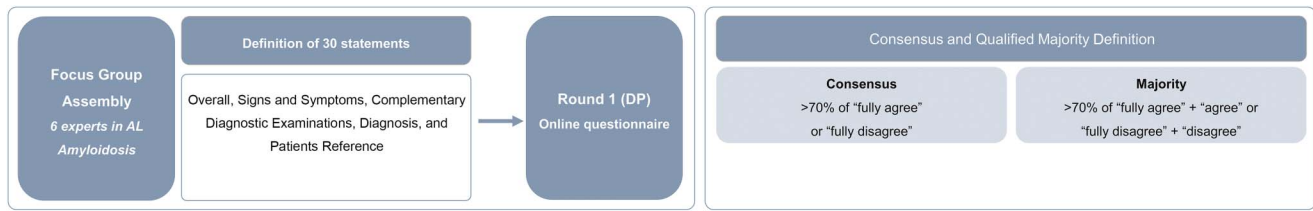
Figure 2. Methodology of the Delphi-like panel (one round only).

and 32% and one statement did not obtain a qualified majority (statement 20). The statements whose disagreement rate was higher are as follows: (16) *When I suspect AL amyloidosis with liver involvement, I should measure alkaline phosphatase levels and perform a liver ultrasound*; (17) *Tests of greater diagnostic specificity are serum and urinary protein immunofixation and free light chain assay*; (20) *Congo Red identification of amyloid substance deposition in abdominal fat biopsy is insufficient for diagnosing AL amyloidosis, even in monoclonal gammopathy*; (21) *Typing of amyloid deposits with immunohistochemistry for light chains is mandatory to confirm AL amyloidosis*; (24) *Bone biopsy with identification of vascular amyloid deposition associated with the presence of monoclonal gammopathy in a patient with cardiac and renal symptoms allows the assumption of AL amyloidosis diagnosis*; and (26) *In patients with cardiac amyloidosis, technetium-99m (99mTC) scintigraphy helps to decide the differential diagnosis between AL amyloidosis and ATTR amyloidosis* (Fig. 3).

Finally, in the scope of "patients referral," most physicians agreed, with only 8.34% disagreeing with the statement, (29) *Timely referral of AL amyloidosis patients to Hemato-Oncology allows for faster diagnosis* (Fig. 3).

Interestingly, the data analysis per medical field discloses an agreement between the results obtained in each medical field and the general results (Figs. 3 and 4). Still, a significant disagreement rate was obtained among the diverse medical specialties considered herein, particularly relating to the following statements: (4) *Monoclonal gammopathy of undetermined significance (MGUS), Multiple Myeloma, and Waldenström's Macroglobulinemia are AL amyloidosis' most frequent precursor diseases*—hematology and general practitioners; and (17) *Tests of greater diagnostic specificity are serum and urinary protein immunofixation and free light chain assay*—hematologists and nephrologists; (18) *Abdominal fat biopsy should be performed with a request for amyloid protein detection and characterization*—general practitioners; and (26) *In patients with*
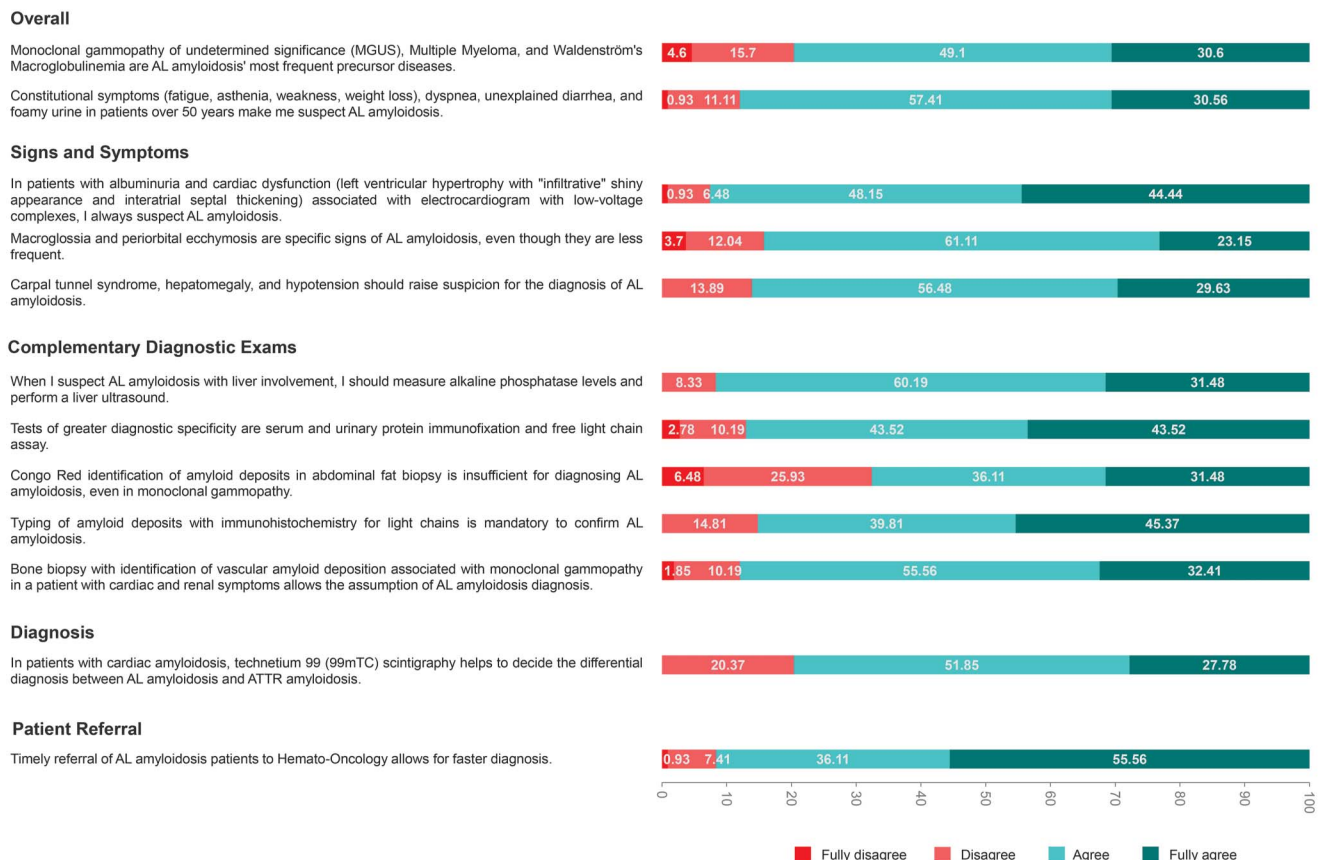

Figure 3. Characterization of the established statements with higher disagreement rates.

cardiac amyloidosis, technetium-99m (99mTC) scintigraphy helps to decide the differential diagnosis between AL amyloidosis and ATTR amyloidosis—nephrologists.

Notably, the level of disagreement among hematologists in statement 20 was 39% (11.1% "fully disagree" and 27.8% "disagree").

Discussion

Although the overall results illustrate an adequate general knowledge of AL amyloidosis, they also highlight the need to raise awareness for this disease. Accordingly, this study revealed a high lack of consensus regarding the diagnosis and referral of patients with AL amyloidosis among different specialties despite the qualified majority obtained in 26 statements.

In this panel, only three statements related to the "overall" characteristics of AL amyloidosis gathered consensus, focusing on the importance of performing an adequate diagnosis to promote proper treatment in the initial stages of the disease and, thus, improve the prognosis.[16] Still, a delayed diagnosis is expected in this pathology, which might result from the nonspecific symptoms associated with the disease.[17,18]

In the "signs and symptoms" section, physicians disagreed on hypothetical clinical signs of AL amyloidosis. Although AL amyloidosis might be unspecific, it has been described that the most common include fatigue, weight loss, and edema.[17,18] Nonetheless, although clinical manifestations of the different forms of amyloidosis depend on the affected organ, the most predominant include heart failure, nephrotic syndrome, hepatomegaly, peripheral neuropathy, autonomic dysfunction, and gastrointestinal dysfunction.[17,19] Occasionally, a constellation of two or more of these symptoms further increases AL clinical suspicion and promotes further investigations. Similarly, previous studies have shown that the monoclonal component can be identified at least four years before the diagnosis in all patients with AL amyloidosis.[20] Thus, all patients with multiple myeloma (MM) or known MGUS should be closely monitored for the development of any amyloid-related organ dysfunction using noninvasive biomarkers for early diagnosis of AL amyloidosis.[21,22] NT-proBNP and albuminuria should be monitored as they can predict cardiac and renal involvement before the manifestation of heart failure or nephrotic syndrome.[21,22] In fact, NT-proBNP can detect cardiac involvement before the appearance of symptoms of cardiac failure in 20% of patients.[23] In patients with Waldenström's macroglobulinemia, special attention should be given to renal involvement because associated IgM AL amyloidosis is one of the predominant glomerular nephropathies.[24] Indeed, not only does an IgM monoclonal component precede the diagnosis of AL amyloidosis in 34% of patients, but AL amyloidosis can also be found after 2–5 years of follow-up of an IgM MGUS in 14% and 8% of cases, respectively.[25]

The results showed that the lowest level of agreement was obtained in "complementary diagnostic exams" and "diagnosis." Specifically, the higher disagreement was obtained in the statement related to the Congo red detection of amyloid deposits in abdominal fat biopsy being insufficient for diagnosing AL amyloidosis. Tissue biopsy and subsequent typing of amyloid must be performed on confirmation of the monoclonal component. Ideally, the affected organ should be biopsied, although not always possible because of the high risk of bleeding or other complications. Congo red staining remains the most common method to detect amyloid; nonetheless, it does not give information regarding the type of amyloid precursor present in the tissue,[26] which is insufficient to elaborate a diagnosis of systemic AL amyloidosis. Mass spectrometry is the standard gold method to identify the type of amyloid deposit and establish a definitive diagnosis.[26,27] In clinical practice, abdominal fat and minor salivary gland are the most accessible biopsy sites, with
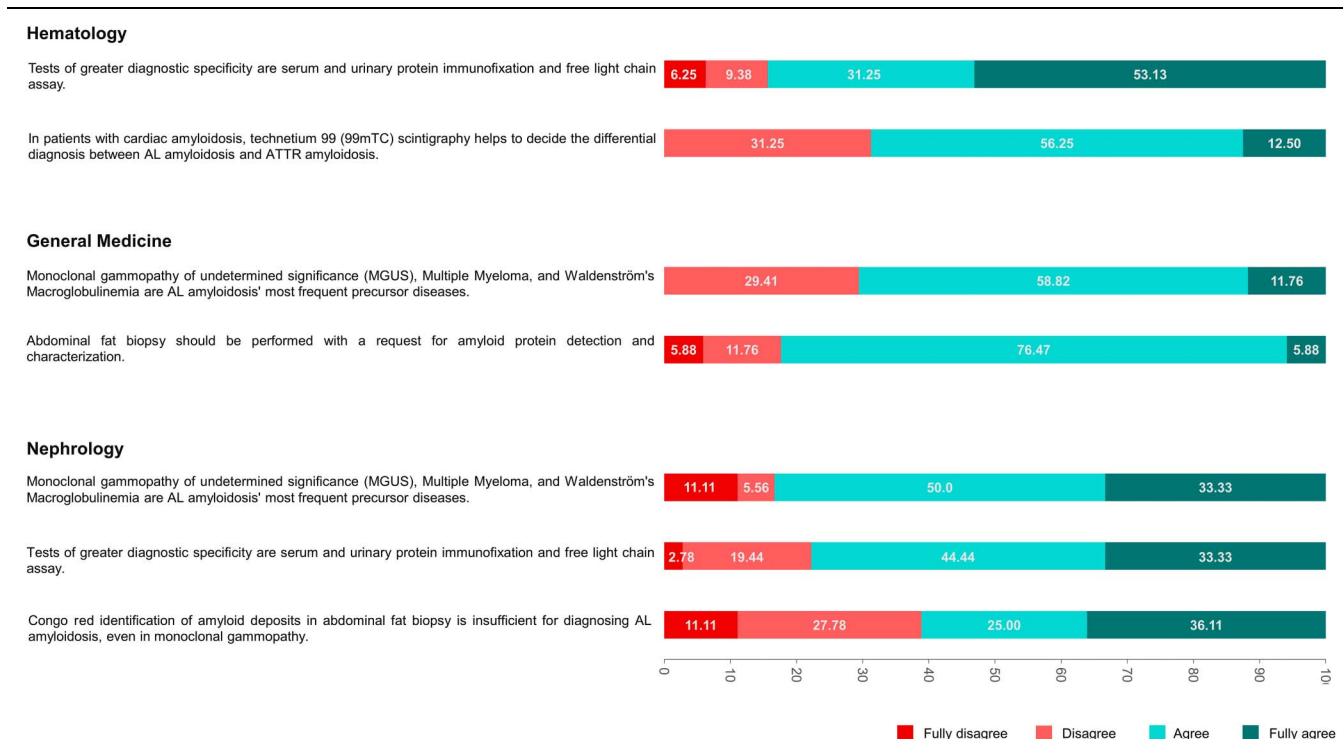

Figure 4. Characterization of the established statements with higher disagreement rates per medical field.

Figure 5. Workflow to improve AL amyloidosis diagnosis and referral to a reference center. BM, bone marrow; BNP, B-type natriuretic peptide; IF, immunofixation; MGUS, monoclonal gammopathy of unknown significance; sFLC, serum free light chain; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis.

81% and 60% diagnostic sensitivity in AL amyloidosis, respectively.[28] Importantly, as the complexity of this technique can lead to false positives, a thorough analysis of fat aspirates is vital to avoid overinterpretation and false-positive diagnoses.[29]

Congo red staining in bone marrow is a convenient alternative during the plasma cell dyscrasia workup with a sensitivity of almost 80% to assume AL amyloidosis.[30] Moreover, it has been reported that Congo red staining of bone marrow biopsy in combination with abdominal fat aspirates approaches a 90%

diagnostic sensitivity and could be used in challenging patients or when it is impossible to biopsy the suspected organ.[31] As described, although mass spectrometry is a technique with high diagnostic accuracy, it is unavailable in most centers because of its complexity. In specialized centers, light microscopy immunohistochemistry can achieve 100% specificity and correctly classify almost all patients with AL amyloidosis.[32,33] Moreover, it is the best method in case of a double amyloid deposit, which is not uncommon in clinical practice.[34] The monoclonal components

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should be considered to avoid misdiagnosis because of their high prevalence in patients with non-AL amyloidosis and their presence in one-fourth to one-third of ATTRwt amyloidoses.[33,35] In complex cases, it is mandatory to analyze DNA to exclude hereditary ATTR and other forms of non-AL amyloidosis or in cases where an overlapping diagnosis is suspected.[33]

Concerning "complementary diagnosis exams," it is essential to highlight the disagreement observed around organ involvement. The most affected organs in amyloidosis AL are the heart and kidneys (70%–80%), but also the liver (15%), soft tissues (15%), peripheral and autonomic nervous system (10%), and gastrointestinal tract (5%).[18,36] Although target-organ biopsy has excellent sensitivity and is needed to confirm AL amyloidosis, the diagnosis can also be suspected and enforced with noninvasive techniques. Several approaches have been reported, including serum ALP, liver enlargement in ultrasound, albuminuria, serum cardiac biomarkers, serum free light chain measurements, and bone marrow analysis.[37] In addition, cardiac imaging, including cardiac resonance, is helpful in the approach of these patients because it can detect early involvement in 28% of patients with regular echocardiograms and high NT-proBNP.[38] Even so, the discordance among physicians regarding using technetium-99m (99mTC) scintigraphy to perform the differential diagnosis between AL and ATTR amyloidosis in the "diagnosis" section is relevant. Specifically, it is fundamental to disclose the techniques that might be used in the future because the discriminatory ability of 99mTc-pyrophosphate scintigraphy (99mTc-PYP) in AL vs. TTR-related cardiac amyloidosis has been validated.[39] Furthermore, it reveals the importance of consolidating the knowledge on which complementary diagnostic examinations are relevant because these may potentiate an earlier and more effective diagnosis, fostering a faster and more successful treatment.[9]

The participants also disagreed about the importance of an early referral of patients with AL amyloidosis to hematooncology. Previous studies have shown that a timely and early referral is associated with faster diagnosis, which improves survival rates. In fact, in referral centers for AL amyloidosis, the survival rates have improved over the years.[40]

The outcome of this Delphi panel reveals an evident lack of consensus in diagnosing and early managing AL amyloidosis among national health professionals. Although all statements categorized as a qualified majority align with the recommendations from a multidisciplinary panel of experts, a more significant number of statements were expected to achieve consensus. The lack of consensus on statements related to signs and symptoms might be due to AL amyloidosis presentation being nonspecific and somewhat dependent on the involved organs. Thus, patients with nonspecific and overlapping symptoms might be easily misjudged, hampering the diagnosis and delaying treatment initiation.[9] Notably, diagnosing AL amyloidosis is a multistep process that should occur without delay, in which the first step (suspicion) is the most critical (Fig. 5).[27] Hence, these results showed the importance of raising awareness of AL amyloidosis across several specialties to foster an effective therapeutic intervention. It is essential to promote familiarity with symptoms (Table 2). Moreover, laboratory biomarkers can raise suspicion as red flags for AL amyloidosis, being critical to define groups of patients who should be frequently screened. Similarly, creating referral centers with access to diagnostic tools and a network of different specialties can promote an early diagnosis and a better treatment approach, increasing the possibility of a better outcome for patients with AL amyloidosis.

Table 2.

When to suspect AL Amyloidosis?

Organ involvement (frequency)	Symptoms and signs
Kidney (70%)	• Asymptomatic proteinuria/nephrotic syndrome
	• Peripheral edema
	• Renal failure
Heart (60%)	• Heart failure with a preserved ejection fraction
	• Thickening of the interventricular septum and ventricular wall
	• Low voltage on electrocardiography
	• Restrictive cardiomyopathy
	• Syncope
	• Arrhythmia or heart block
	• Low-flow, low-gradient aortic stenosis
	• Elevation of N-terminal serum brain natriuretic peptide (BNP)
	• Dyspnea
	• Fatigue
Liver (17%)	• Hepatomegaly
	• Cholestatic pattern with elevated alkaline phosphatase
Gastrointestinal tract (10%)	• Malabsorption
	• Chronic diarrhea
	• Weight loss
Autonomic nervous system (15%)	• Lethargy
	• Postural hypotension
	• Gastroparesis and constipation
	• Gastric-emptying disorder, pseudo-obstruction, voiding dysfunction
	• Erectile dysfunction
Peripheral neuropathy (15%)	• Symmetric lower extremity sensorimotor polyneuropathy (ascending, symmetric, and small fiber/axonal)
	• Carpal tunnel syndrome
Soft tissues (15-35%)	• Macroglossia
	• Periorbital purpura
	• Waxy thickening
	• Subcutaneous nodules or plaques
	• Submandibular claudication
	• Submandibular glands swelling
	• Xerostomia
	• Shoulder pad sign
	• Bleeding (factor X deficiency, acquired von Willebrand)

Conclusively, this study revealed the existence of more comprehensive knowledge about the signs and symptoms, leading to AL amyloidosis suspicion than its diagnosis. An optimized strategy for AL amyloidosis early diagnosis, transversal to several medical fields, is urgently needed.

Author Contributions

All authors contributed significantly to the design and organization of the work, interpretation of the data, preparation and critical review of the manuscript, and approval of the final version.

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Conflicts of interest

R. Bergantim: Amgen and BMS (Consultancy, Research Funding, Speaker Fee), Janssen and Takeda (Consultancy, Speaker Fee). I. Tavares: Janssen (Consultancy). G.V. Esteves: Pfizer, AbbVie, Sanofi, and Janssen (Consultancy, Speaker Fee). The remaining authors have no conflicts to declare.

Presentation

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