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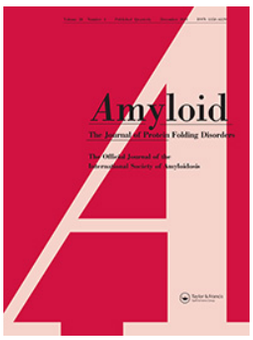

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RESEARCH ARTICLE

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# Amyloidosis from the patient perspective: the French daily impact of amyloidosis study

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**ABSTRACT**

**Background:** Amyloidosis is a complex group of rare conditions. For patients, amyloidosis is severely debilitating: physically and psychologically. Currently, data are lacking to evaluate the medical, economic, and social burden of systemic amyloidosis.

**Objective:** To analyse the patient burden according to the main types of systemic amyloidosis.

**Methods:** The French Daily Impact of Amyloidosis study was an observational, cross-sectional and non-interventional study. Adults diagnosed with light chain (AL), transthyretin (ATTR), amyloid A (AA) and other rare forms of amyloidosis were eligible. Data regarding amyloidosis prevalence, diagnosis, management, and impact on everyday life were collected using a study-specific survey built by the Association Française Contre l'Amylose (AFCA) and the four French National Referral Centres for Amyloidosis.

**Results:** A total of 603 patients, predominantly male (65%) with an average age of 66.8 years, including 170 AL, 224 ATTRv, 109 ATTRwt and 25 AA amyloidosis patients, completed the study-specific survey. The median delay from presentation to confirmed diagnosis was 27.4 months but varied according to amyloidosis type. Patients before diagnosis had breathlessness (49%), tingling sensation (33%), pain (28%), difficulty in walking (28%) and weight loss (22%). Amyloidosis was most frequently suspected (49%) and confirmed (57%) in local hospitals but managed in French amyloidosis referral centres (58%). Patients often reported problems with mobility, usual activities, pain/discomfort and anxiety/depression, but not with self-care.

**Conclusions:** Systemic amyloidosis severely impacts daily life. The delay to confirmed amyloidosis diagnosis needs to be reduced. Early, effective treatment is required to optimise patient benefits.

**Abbreviations:** AA: amyloid A amyloidosis; AFCA: "Association Française contre l'Amylose" (the French association engaged in the fight against amyloidosis); AL: immunoglobin light chain amyloidosis; ATTR: transthyretin amyloidosis; ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; CHU: "Centre Hospitalier Universitaire" (University Hospital Centre); EQ-5D: EuroQol-5D questionnaire; MDPH: "Maison Départementale des Personnes Handicapées" (French department for handicapped people); TTR: transthyretin

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AL amyloidosis; transthyretin amyloidosis; AA amyloidosis; quality of life; diagnosis duration

## Introduction

Amyloidosis is not only a rare and complex group of diseases but is also a debilitating and life-threatening disease associated with severe physical symptoms that affect daily activities, including work. These difficulties make patients reliant on others for subsistence. In addition to physical symptoms, these patients face emotional and psychological issues that impact their lives and those of their family and friends [1,2].

Amyloidosis is characterised by the accumulation of amyloid fibrils formed by the misfolding of various proteins. Currently, more than 30 proteins have been implicated in amyloidosis, although only 14 of these result in systemic amyloidosis [3]. Misfolded amyloid precursors form insoluble amyloid fibrils that accumulate in tissues

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Supplemental data for this article can be accessed here.

and organs. Amyloid fibrils display typical dichroism and birefringence under polarised light after Congo red staining.

The main types of systemic amyloidosis include immunoglobin light chain (AL), wild-type transthyretin (ATTRwt), hereditary transthyretin amyloidosis (ATTRv) with neurologic, cardiologic, or mixed (neurologic and cardiac) phenotypes and serum amyloid A (AA) amyloidosis. Misfolding of the monoclonal light chain protein, produced in the bone marrow, results in AL amyloidosis [4,5]. While ATTR amyloidosis results from the misfolding of transthyretin (TTR), mainly produced in the liver, and comprises two subtypes: ATTRwt and ATTRv. Patients with ATTRv have inherited one of more than a hundred known amyloidogenic mutations of the *TTR* gene [4,5]. In contrast, ATTRwt is an acquired age-related disease. AA amyloidosis results from misfolding of the serum amyloid A protein produced in the liver [4,5].

Patients with systemic amyloidosis frequently present with various symptoms, including fatigue and weight loss, with signs of organ dysfunction, that can include heart and kidney failure, and peripheral neuropathy [6,7]. Indeed, clinical signs indicative of amyloid deposits, such as proteinuria and carpal tunnel syndrome, are frequently present before a diagnosis of amyloidosis is confirmed histologically.

The diagnosis and the confirmation of the amyloidosis type requires multidisciplinary expertise and can be delayed in non-expert centres [6,8,9]. Depending on the type of amyloidosis various tissues/organs may be affected, and patients may present with a wide range of symptoms. A correct diagnosis is critical in amyloidosis management. For example, AL and AA patients typically present with proteinuria, kidney dysfunction and/or heart failure; while those with ATTR often present with peripheral neuropathy and/or heart failure [7]. In AL and ATTR, treatments that effectively slow progression, stabilise, or potentially improve heart, kidney and neurological function are available [10]. However, these therapies are distinct making timely and correct diagnosis of amyloidosis critical. Importantly, in certain types of amyloidosis early diagnosis and treatment can prevent organ failure [3]. However, if patients are not treated appropriately and rapidly, excessive amyloid deposition results in organ dysfunction and eventually organ failure [7]. Recent diagnostic advances in genetic screening, heart imaging and disease-specific biological test, particularly those used to identify and quantify the amyloid precursor, have improved diagnosis. However, despite these advances, amyloidosis is believed to be largely underdiagnosed [6]. Furthermore, in those patients diagnosed, the delay between presenting symptoms and confirmed diagnosis remains long. Indeed, a cross-sectional analysis of data from 341 AL amyloidosis patients in the USA, reported that about 43% were without a diagnose 1 year after initial symptoms [1]. Also, in cardiac ATTRwt patients, the median time interval from initial cardiac symptoms to diagnosis was reported to be 39 months, with 42% of patients without confirmed diagnosis after 4 years [6,11].

Our objective, based on a large French cohort, was to collect data about amyloidosis patient management. Using these data, we wanted to evaluate the impact of amyloidosis, from the patient's perspective, and to explore the extended impact on families, friends and society.

## Methods

### Study design

The French Daily Impact of Amyloidosis study was designed as an observational, cross-sectional and non-interventional study. This study was conducted by the 'Association Française Contre l'Amylose' (AFCA) – the French association engaged in the fight against amyloidosis – in partnership with the French referral centres for amyloidosis dedicated to familial amyloid polyneuropathies (NNerf; the University Hospital [CHU] Bicêtre [Kremlin-Bicêtre]), AL amyloidosis (CHU Limoges and CHU Poitiers), inflammatory amyloidosis (CEREMAIA; Tenon Hospital [Paris]) and cardiac amyloidosis (Reseau Amylose Mondor; CHU Mondor [Créteil]); and the corresponding national networks for immunologic and haematological diseases (MARIH), hereditary and rare cardiac diseases (CARDIOGEN), rare neuromuscular diseases (FILNEMUS), and rare immune and autoinflammatory diseases (FAI2R).

Amyloidosis patients registered in the AFCA and referral centres' databases were solicited *via* letters and emails to participate in the study. Registered or new patients who presented at participating centres were also proposed the study. Patients older than 18 years and diagnosed with amyloidosis were eligible. A healthcare professional explained the study and supportive documents were distributed to the patients. Once informed, patients provided oral consent to participate in the study.

### Data collection

Between February to June 2019, data were collected from patients using a study-specific survey (Figure S1). The survey was compiled by an expert committee was comprised of key-role players in amyloidosis management in France, including expert patient representatives, representatives from the amyloidosis associations, and physicians treating amyloidosis. The survey contained several sections, including the standardised EuroQol-5D (EQ-5D) questionnaire. All data collected and analysed were de-identified. The study-specific survey was approved by a French ethics committee: 'Comité de Protection des Personne Sud-Ouest et Outre Mer III', Bordeaux.

### Study objectives

Our objective was to use the collect data to describe the stages of amyloidosis care: diagnosis, therapeutic management and follow up. We studied the interaction between patients and healthcare professionals (doctors, nurses, social workers, etc.). Furthermore, we investigated the patient's

perspective concerning administrative difficulties, particularly those related to healthcare, how they perceived their amyloidosis and its influence on their quality of life.

### Statistical analysis

The patients who completed the study-specific survey were classified by type of amyloidosis into seven groups: AL, ATTRv with neuropathy, ATTRV with cardiomyopathy, ATTRwt, AA, other hereditary amyloidosis or other/unknown for those with other types of amyloidosis or for those that did not indicate a type of amyloidosis in the survey. Responses to the survey were calculated as a percentage of the study population without adjusting for missing data. Concerning the EQ-5D data, the overall score, as well as the percentages of responders for each of the five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) are presented. Continuous data are described as means. All categorical data are described as the number of patients with percentages. The study was designed as a non-comparative study. Therefore, no comparative or subgroup analyses were performed.

## Results

### Participants and data collection

Between January 2019 and July 2019, 603 patients, completed the study-specific survey at one of five participating French hospitals: CHU Bicêtre (Paris), CHU Jean Bernard (Poitier), CHU Mondor (Créteil), CHU Tenon Hospital (Paris) and CHU Dupuytren (Limoges). The patient baseline characteristics are shown in Table 1. The patients were mainly men (65%) and with an average age of 66.8 years. Patients diagnosed with AL were younger (55.7 years) than the overall amyloidosis population. While patients diagnosed with ATTRwt amyloidosis were to a larger extent male (84%) and on average older (77.6 years). Patients diagnosed with AA amyloidosis were also older (75.7 years). Most patients lived as couples (76%) with children (87%). Patients were mostly not working or retired (67%), only 19% were employed. However, patients in the ATTRv with neuropathy and other types of hereditary amyloidosis were more frequently employed (37% and 40%, respectively) and less frequently not working or retired (47% and 52%, respectively). Interestingly, 61% of patients lived in areas with fewer than 50,000 inhabitants: medium or small towns or rural areas.

### Diagnoses of amyloidosis

The average time interval from the initial symptoms until a confirmed amyloidosis diagnosis in the overall population was 27.4 months: 21.7 months for AL, 45.6 months for ATTRv (with neuropathy), 31.8 months for ATTRv (with cardiopathy), 19.6 months for ATTRwt, 19.0 months for AA patients, 39.2 months for other hereditary and 15.8 months for those with amyloidosis of unknown type (Figure 1).

The most frequent symptoms occurring preceding amyloidosis diagnosis were breathlessness (49%), tingling (33%), pain (28%), difficulty in walking (28%) and weight loss (22%) (see Figure 2). Breathlessness was more common in the ATTRv with cardiomyopathy (72%) and ATTRwt (79%)

**Table 1.** Baseline characteristics of patients.

| | | Amyloidosis groups | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ATTRv ($n = 224$) | | | | | |
| Variables, *n* (%) | All patients | AL | ATTRv with neuropathy | ATTRv with cardiopathy | ATTRwt | AA | Other hereditary | Other or unknown |
| *n* (%) | 603 (100) | 170 (28) | 125 (21) | 99 (16) | 109 (18) | 25 (4) | 24 (4) | 51 (8) |
| Mean age, years | 66.8 | 55.7 | 65.8 | 66.9 | 77.6 | 75.7 | 62.3 | |
| Sex, *n* (%) | | | | | | | | |
| Male | 390 (65) | 103 (61) | 71 (57) | 62 (63) | 92 (84) | 13 (52) | 15 (63) | 34 (67) |
| Female | 208 (34) | 67 (39) | 54 (43) | 35 (35) | 16 (15) | 12 (48) | 9 (38) | 15 (29) |
| Missing data | 5 (1) | 0 (0) | 0 (0) | 2 (2) | 1 (1) | 0 (0) | 0 (0) | 2 (4) |
| Living situation, *n* (%) | | | | | | | | |
| Alone | 106 (18) | 28 (16) | 25 (20) | 14 (14) | 18 (17) | 6 (24) | 1 (4) | 14 (27) |
| Couple | 459 (76) | 135 (79) | 88 (70) | 81 (82) | 90 (83) | 16 (64) | 23 (96) | 26 (51) |
| Retirement home | 3 (1) | 2 (1) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 (2) |
| Others | 13 (2) | 3 (2) | 5 (4) | 0 (0) | 0 (0) | 1 (4) | 0 (0) | 4 (8) |
| Has child/children, *n* (%) | 523 (87) | 150 (88) | 102 (82) | 89 (90) | 100 (92) | 19 (76) | 23 (96) | 40 (78) |
| Professional situation, *n* (%) | | | | | | | | |
| Employed | 113 (19) | 24 (14) | 46 (37) | 14 (14) | 7 (6) | 6 (24) | 10 (42) | 6 (12) |
| Student/apprentice | 3 (1) | 0 (0) | 1 (1) | 0 (0) | 0 (0) | 1 (4) | 1 (4) | 0 (0) |
| Had to stop work/ invalidity | 69 (11) | 27 (16) | 18 (14) | 14 (14) | 3 (3) | 3 (12) | 1 (4) | 3 (6) |
| Retired or not working | 406 (67) | 118 (69) | 59 (47) | 70 (71) | 98 (90) | 9 (36) | 12 (50) | 40 (78) |
| Unemployed | 7 (1) | 1 (1) | 1 (1) | 0 (0) | 1 (1) | 4 (16) | 0 (0) | 0 (0) |
| Living environment, *n* (%) | | | | | | | | |
| Paris and its suburbs | 136 (23) | 27 (16) | 35 (28) | 19 (19) | 28 (26) | 8 (32) | 4 (17) | 15 (29) |
| Large city (more than 100,000 inhabitants) | 41 (7) | 9 (5) | 7 (6) | 10 (10) | 8 (7) | 1 (4) | 3 (13) | 3 (6) |
| Large town (50,000 to 90,000) | 49 (8) | 18 (11) | 12 (10) | 5 (5) | 6 (6) | 1 (4) | 0 (0) | 7 (14) |
| Medium town (10,000–49,999) | 101 (17) | 32 (19) | 23 (18) | 15 (15) | 18 (17) | 6 (24) | 4 (17) | 3 (6) |
| Small town (2000–9999) | 135 (22) | 39 (23) | 26 (21) | 25 (25) | 23 (21) | 7 (28) | 8 (33) | 7 (14) |
| Rural area (less than 2000) | 130 (22) | 42 (25) | 22 (18) | 23 (23) | 26 (24) | 0 (0) | 5 (21) | 12 (24) |

AA: serum amyloid A amyloidosis; AL: immunoglobin light chain amyloidosis; ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis.

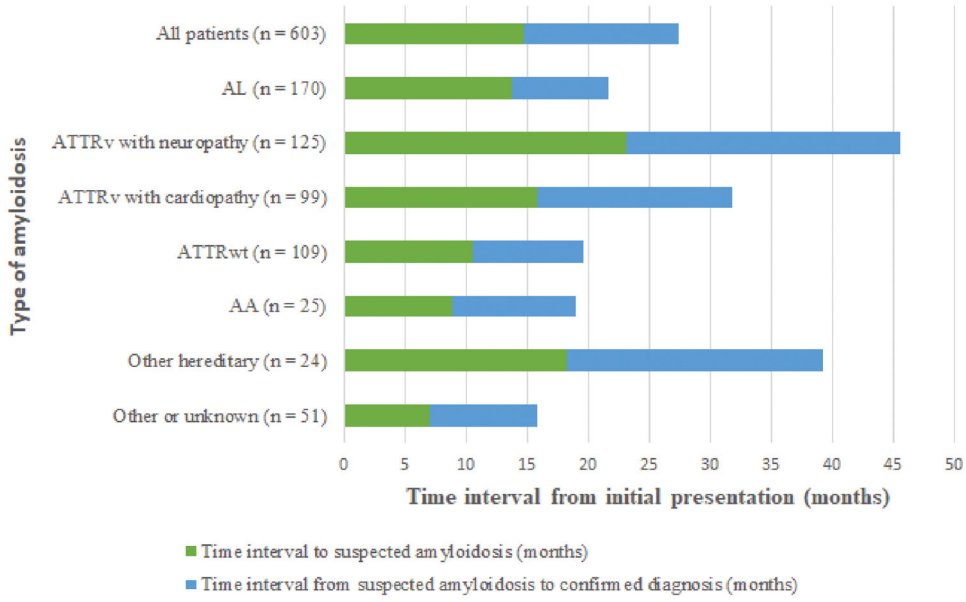


**Figure 1.** Time interval from initial amyloidosis symptoms to suspected diagnosis (shown in green) and then time interval to confirmation of amyloidosis subtype (shown in blue). AA: serum amyloid A amyloidosis, AL: immunoglobin light chain amyloidosis, ATTRv: hereditary transthyretin amyloidosis, ATTRwt: wild-type transthyretin amyloidosis.

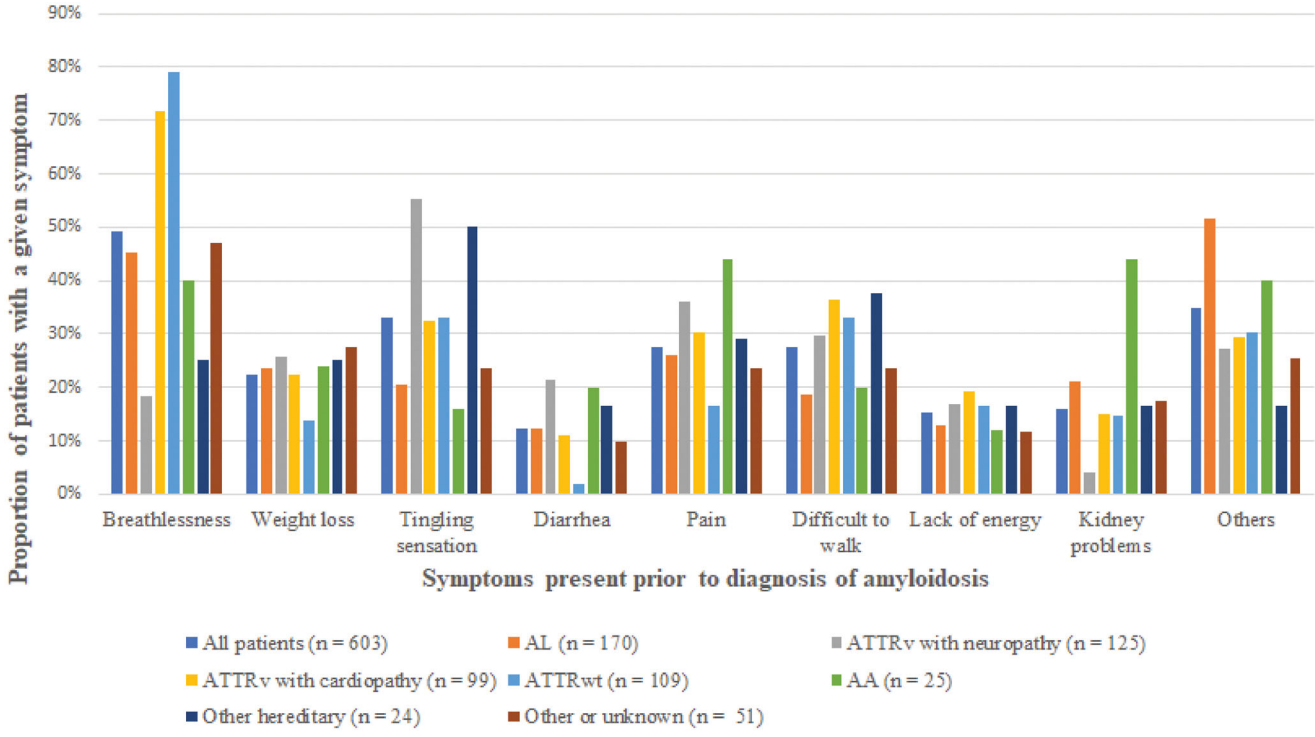


**Figure 2.** The symptoms present prior to diagnosis in the overall population by type of amyloidosis. AA: serum amyloid A amyloidosis, AL: immunoglobin light chain amyloidosis, ATTRv: hereditary transthyretin amyloidosis, ATTRwt: wild-type transthyretin amyloidosis.

groups. Tingling was more common in the ATTRv with neuropathy (55%) and hereditary other (50%) groups. Interestingly, 44% of AA amyloidosis patients initially had kidney problems as did 16% in the overall population.

The diagnosis of systemic amyloidosis was first suspected by hospital physicians (49%) then specialists in private practice (23%), followed by referral centre physicians (11%) and general practitioners (6%) (see Table 2). However, the diagnosis was mostly confirmed by hospital physicians (57%) and to a lesser extent by those in referral centres (27%). During the visit, when told that they had amyloidosis, 69% of patients indicated that the duration of the consultation was sufficient (see Table 3). Furthermore, most patients indicated that the healthcare professional took sufficient time to explain (78%), listen (78%) and provide the necessary information (74%). Also, 74% of patients indicated that they asked the question they wanted, 73% felt supported and 74% understood the

Table 2. Doctors that suspected and confirmed amyloidosis diagnoses.

| | | Amyloidosis groups | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ATTRv ($n$ = 24) | | | | | |
| Variables, $n$ (%)<br>$N$ | All patients<br>603 | AL<br>170 | ATTRv with neuropathy<br>125 | ATTRv with cardiopathy<br>99 | ATTRwt<br>109 | AA<br>25 | Other hereditary<br>24 | Other or unknown<br>51 |
| General practitioner | 40 (7) | 11 (6) | 8 (6) | 8 (8) | 2 (2) | 3 (12) | 2 (8) | 6 (12) |
| Specialist (private practice) | 136 (23) | 38 (22) | 16 (13) | 25 (25) | 44 (40) | 2 (8) | 5 (21) | 6 (12) |
| Hospital physician | 296 (49) | 104 (61) | 42 (34) | 44 (44) | 53 (49) | 17 (68) | 9 (38) | 26 (51) |
| Referral centre physician | 67 (11) | 7 (4) | 31 (25) | 12 (12) | 5 (5) | 2 (8) | 4 (17) | 6 (12) |
| Which doctor confirmed the amyloidosis? | | | | | | | | |
| General practitioner | 5 (1) | 1 (1) | 1 (1) | 1 (1) | 1 (1) | 0 (0) | 0 (0) | 1 (2) |
| Specialist (private practice) | 39 (6) | 12 (7) | 4 (3) | 7 (7) | 8 (7) | 3 (12) | 2 (8) | 3 (6) |
| Hospital physician | 343 (57) | 107 (63) | 58 (46) | 60 (61) | 60 (55) | 16 (64) | 12 (50) | 30 (59) |
| Referral centre physician | 163 (27) | 41 (24) | 44 (35) | 26 (26) | 32 (29) | 4 (16) | 8 (33) | 8 (16) |

AA: serum amyloid A amyloidosis, AL: immunoglobin light chain amyloidosis, ATTRv: hereditary transthyretin amyloidosis, ATTRwt: wild-type transthyretin amyloidosis.

information provided. After diagnosis, to obtain more information, 65% of patients consulted the internet, 36% read brochures and magazines and 13% contacted a patient organisation (Table S1).

### *Amyloidosis management during follow up*

Data concerning amyloidosis management during follow up are shown in Tables 4 and Table S1. After being diagnosed, 58% of patients were monitored in one of the French amyloidosis referral centres. The frequency of visits was once yearly in 16%, twice yearly in 36%, and thrice yearly in 14% of patients. In 68% of patients, a multidisciplinary team was implicated in the amyloidosis management. Furthermore, 71% of patients felt implicated in decisions concerning their amyloidosis management. On average during the preceding 12 months: about 8.9 biological tests, 4.0 imagery assessments and 2.0 biopsies were performed for each patient. Furthermore, during the same period, 52% had been hospitalised, on average 3.0 time, and 19% received emergency services, on average 2.3 times. Thirty-one percent of patients benefitted from a nurse at home. Patients had sessions or consulted with the following healthcare professionals: physiotherapists (21%), psychotherapists (13%); nutritionists (22%), homeopaths (3%), sophrologists (3%), and therapeutic patient educator (11%). Of these, 75% of patients reported that these sessions/consultations were beneficial.

### *The influence of amyloidosis on everyday life*

Amyloidosis patients reported the following side-effects: tiredness (67%), pain (56%), disturbed sleep (56%) and loss of appetite (46%); and infections (34%) (Table S2). Most patients reported feeling limited with everyday life (63%), strenuous activities (70%), sports and hobbies (62%) and changing positions (61%), such as standing up or bending over. Most patients (75%) felt that their amyloidosis was a handicap, 74% were worried about the future, 59% felt angry or anxious and 58% were discouraged. Sexual desire had reportedly decreased in 72% of patients and that of their partners in 59%. Forty-nine percent of patients believed that their amyloidosis affected their relationship with family and friends. Overall, amyloidosis severely affected quality of life since 69% thought about their disease daily, 69% felt never at peace, 66% did not want to plan for future. However, 85% felt grateful for their support group.

The mean EQ-5D score, with a maximum of 100, was 58.8 (standard deviation: 2.1, range: 5–100). Most patients indicated that they experienced difficulties (in all levels) with mobility (62%), usual activities (67%), pain/discomfort (80%) and anxiety/depression (58%) (Figure 3 and Table S3). It is notable that 31% of patients reported difficulties with self-care.

### *Impact of amyloidosis on finances, work and family*

Amyloidosis not only personally affects patients but also has a broader impact on daily life, including finances, work and family life. The French department for handicapped people ('Maison Départementale des Personnes Handicapées' [MDPH]) provides aid to handicapped individuals. In our study population, 40% of the patients believed that they were well-informed concerning their rights to receive aid; 78% had applied for permission to use handicapped parking, and 30% had applied for handicapped worker status (Tables 5 and Table S4). Furthermore, 33% of patients working at diagnosis had to stop work and 10% had to modify their work due to amyloidosis. The MDPH application took on average 6.8 months to process. Most patients, 74% have private medical aid to complement standard French healthcare benefits. Over and above healthcare costs, patients estimate that their amyloidosis costed them on average 656.70 euros per year. Only 30% of patients were currently working. A family member assisted 31% of patients daily and 16% occasionally. The family member was the spouse in 78% of patients. Twelve percent of patients indicate that their amyloidosis impacted the family member's work: requiring the family member to work fewer hours, to take holidays, or to stop working.

## Discussion

This is the largest national survey on amyloidosis to our knowledge performed by the complementary actions of a

**Table 3.** Amyloidosis diagnosis from the patient's perspective.

| | | Amyloidosis groups | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ATTRv ($n = 224$) | | | | | |
| Variables, *n* (%)<br>*N* | All patients<br>603 | AL<br>170 | ATTRv with neuropathy<br>125 | ATTRv with cardiopathy<br>99 | ATTRwt<br>109 | AL<br>25 | Other hereditary<br>24 | Other or unknown<br>51 |
| When you were told that you had amyloidosis, the patient considered that … | | | | | | | | |
| The doctor took sufficient time to explain | 473 (78) | 143 (84) | 99 (79) | 79 (80) | 84 (77) | 19 (76) | 18 (75) | 31 (61) |
| The doctor took sufficient time to listen | 471 (78) | 138 (81) | 98 (78) | 80 (81) | 84 (77) | 19 (76) | 17 (71) | 35 (69) |
| The doctor provided the information that they required | 447 (74) | 128 (75) | 95 (76) | 77 (78) | 81 (74) | 15 (60) | 16 (67) | 35 (69) |
| The patient asked the questions that they wanted to | 445 (74) | 125 (74) | 90 (72) | 80 (81) | 83 (76) | 18 (72) | 18 (75) | 31 (61) |
| The patient felt supported | 443 (73) | 129 (76) | 96 (77) | 77 (78) | 74 (68) | 16 (64) | 17 (71) | 34 (67) |
| The patient understood the information from the doctor | 447 (74) | 129 (76) | 99 (79) | 75 (76) | 77 (71) | 20 (80) | 17 (71) | 30 (59) |
| The patient was so overwhelmed that he/she did not understand the information from the doctor | 111 (18) | 30 (18) | 19 (15) | 20 (20) | 21 (19) | 7 (28) | 4 (17) | 10 (20) |
| When diagnosis, the patient found the visit duration … | | | | | | | | |
| Sufficient | 417 (69) | 119 (70) | 89 (71) | 74 (75) | 75 (69) | 15 (60) | 19 (79) | 26 (51) |
| Insufficient | 6 (1) | 2 (1) | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 1 (4) | 1 (2) |
| Does not know | 75 (12) | 17 (10) | 5 (4) | 14 (14) | 20 (18) | 5 (20) | 1 (4) | 13 (25) |
| Missing data | 105 (17) | 32 (19) | 31 (25) | 9 (9) | 14 (13) | 5 (20) | 3 (13) | 11 (22) |

AA: serum amyloid A amyloidosis; AL: immunoglobin light chain amyloidosis; ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis.

**Table 4.** Amyloidosis healthcare after diagnosis.

| | | Amyloidosis groups | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ATTRv ($n = 224$) | | | | | |
| Variables<br>*N* | All patients<br>603 | AL<br>170 | ATTRv with neuropathy<br>125 | ATTRv with cardiopathy<br>99 | ATTRwt<br>109 | AA<br>25 | Other hereditary<br>24 | Other or unknown<br>51 |
| Healthcare consultations after diagnosis | | | | | | | | |
| The doctor consulted works in … | | | | | | | | |
| A referral centre | 350 (58) | 91 (54) | 89 (71) | 65 (66) | 57 (52) | 8 (32) | 16 (67) | 24 (47) |
| A specialised centre | 82 (14) | 32 (19) | 10 (8) | 11 (11) | 15 (14) | 5 (20) | 3 (13) | 6 (12) |
| Neither of the above | 25 (4) | 7 (4) | 3 (2) | 4 (4) | 4 (4) | 2 (8) | 1 (4) | 4 (8) |
| Does not know | 93 (15) | 28 (16) | 10 (8) | 12 (12) | 21 (19) | 6 (24) | 2 (8) | 14 (27) |
| Frequency of visits with doctor | | | | | | | | |
| Once a year | 99 (16) | 15 (9) | 40 (32) | 11 (11) | 14 (13) | 5 (20) | 5 (21) | 9 (18) |
| Twice a year | 217 (36) | 44 (26) | 52 (42) | 47 (47) | 48 (44) | 4 (16) | 6 (25) | 16 (31) |
| Thrice a year | 83 (14) | 31 (18) | 8 (6) | 12 (12) | 18 (17) | 6 (24) | 7 (29) | 1 (2) |
| Other | 146 (24) | 67 (39) | 11 (9) | 23 (23) | 17 (16) | 7 (28) | 4 (17) | 17 (33) |
| Medical resources used | | | | | | | | |
| Benefitted from a nurse at home | | | | | | | | |
| Yes | 187 (31) | 77 (46) | 21 (17) | 30 (32) | 20 (19) | 9 (38) | 9 (38) | 21 (41) |
| Regularly | 103 (55) | 48 (62) | 6 (29) | 14 (47) | 9 (45) | 4 (44) | 5 (56) | 17 (81) |
| Benefitted from material reimbursed by the French healthcare system (orthopaedics, walking stick, walking frame, wheelchair … ) | 127 (21) | 31 (19) | 28 (23) | 15 (50) | 14 (13) | 4 (17) | 9 (38) | 26 (51) |
| Did the patient have sessions or consult with the following healthcare professionals? | | | | | | | | |
| Physiotherapist | 127 (21) | 31 (18) | 29 (23) | 30 (30) | 15 (14) | 5 (20) | 9 (38) | 8 (16) |
| Psychologist | 77 (13) | 22 (13) | 27 (22) | 16 (16) | 1 (1) | 3 (12) | 3 (13) | 5 (10) |
| Nutritionist | 134 (22) | 53 (31) | 10 (8) | 27 (27) | 18 (17) | 9 (36) | 2 (8) | 15 (29) |
| Homoeopath | 21 (3) | 10 (6) | 2 (2) | 2 (2) | 3 (3) | 1 (4) | 1 (4) | 2 (4) |
| Sophrologist | 16 (3) | 10 (6) | 3 (2) | 0 (0) | 2 (2) | 0 (0) | 0 (0) | 1 (2) |
| Patient Educational Program | 65 (11) | 19 (11) | 15 (12) | 15 (15) | 8 (7) | 0 (0) | 6 (25) | 2 (4) |
| The consultations/sessions helped the patient with daily life | 49 (75) | 15 (79) | 12 (80) | 14 (93) | 4 (50) | 0 (0) | 4 (67) | 0 (0) |

AA: serum amyloid A amyloidosis; AL: immunoglobin light chain amyloidosis; ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis.

patients' association (AFCA) and four referral centres for amyloidosis. In 2005, the French amyloidosis referral centres were created with the help of the AFCA to improve diagnosis and care for amyloidosis patients. Since then, major advances in the treatment of the three main types of amyloidosis have been developed.

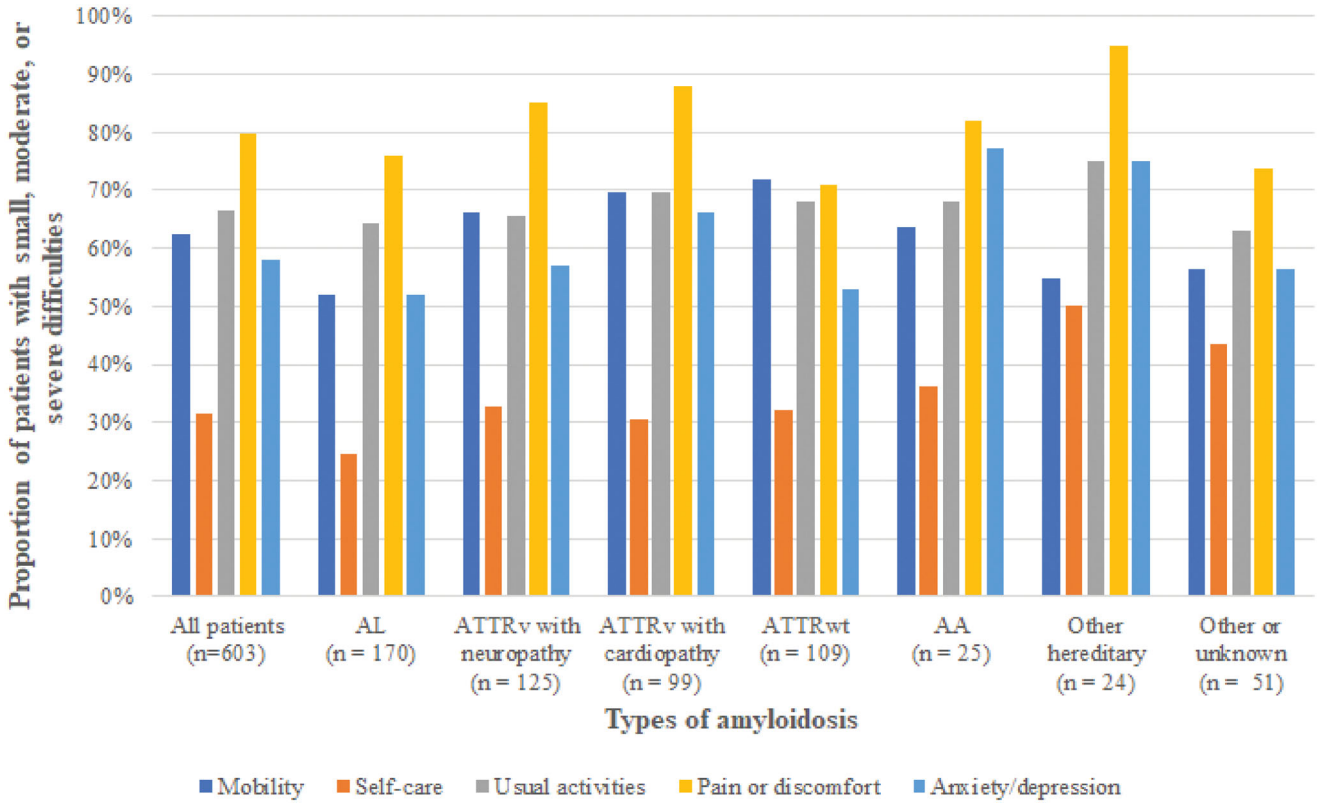


**Figure 3.** Proportion of patients with difficulties (small/moderate/severe) in each dimension of the EQ-5D instrument in all patients and according to the types of amyloidosis.

Our results show that diagnosis and subsequent confirmation of amyloidosis usually takes a long time. Indeed, this process takes on average 19–21.7 months for patients with AL, ATTRwt and AA to more than 31.8 months for those with ATTRv with neuropathy or cardiomyopathy, or other hereditary amyloidosis. We also observed that amyloidosis was associated with debilitating symptoms, including breathless, pain and difficulty in walking, even prior to diagnosis. Ultimately, amyloidosis severely impacts patient quality of life.

### *Amyloidosis diagnosis, a challenging step*

Currently, amyloidosis diagnosis is a challenging multistep process. Consequently, diagnosis is often incorrect and delayed. A retrospective analysis of 82 patients found that the median delay to diagnosis, defined as the time interval between first symptom and a diagnostic biopsy, was 21.7 months (IQR: 11.3–55.4) [9]. This is similar to the 28.4 months, on average, required in our study, for a confirmed diagnosis of amyloidosis. Bishop et al. reported that extended delay in diagnosis was associated with the presence of carpal tunnel syndrome, a pacemaker, age younger than 70 years, symptoms of neuropathy and chronic kidney disease [9]. But most noteworthy, as in our study, the delay depended on the type of amyloidosis: the median delay was 14.6 (8.8–21.3) for patients diagnosed with AL amyloidosis and 34.4 months (15.2–71.8) for those diagnosed with ATTR amyloidosis. Ladefoged et al. assessed 50 patients diagnosed with ATTRwt and found a median delay of 13 months (range 2–47) [8]. In addition, delayed diagnosis of ATTRwt beyond 3 months was associated with worse symptoms and left-ventricular diastolic dysfunction at diagnosis [8].

### *Improving healthcare professionals' knowledge about amyloidosis*

Although symptoms of amyloidosis are highly varied, making amyloidosis diagnosis difficult, there is also a need for increased awareness among healthcare professionals. A recent survey, conducted in Swiss cardiologists, found that knowledge about diagnostic tests required to differentiate types of amyloidosis varied greatly. Most notably, many cardiologists were not familiar with radiolabeled bone scintigraphy: a non-invasive diagnostic tool for cardiac ATTR amyloidosis [12]. Furthermore, to reduce the delay in diagnosis observed, Lane et al. propose that cardiac magnetic resonance imagery and bone scintigraphy should be systematically performed in patients with cardiomyopathy and heart failure of unknown origin [11]. Ihne et al. suggest that once amyloidosis is suspected these patients should be immediately referred to specialised centres for diagnosis and treatment [6]. In our study, in most patients, hospital physicians (49%) and specialists in private practice (23%) were the first to suspect amyloidosis, as may be expected. However, 57% of diagnoses were confirmed in hospitals and only 27% in the amyloidosis referral centres (27%). We agree with Ihne et al., that earlier referral to specialised centres would decrease the diagnostic delay and be beneficial for patients.

**Table 5.** Impact of amyloidosis on the patient's daily life.

| | | Amyloidosis groups | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | ATTRv ($n = 224$) | | | | | |
| Variables<br>*N* | All patients<br>603 | AL<br>170 | ATTRv with neuropathy<br>125 | ATTRv with cardiopathy<br>99 | ATTRwt<br>109 | AA<br>25 | Other hereditary<br>24 | Other or unknown<br>51 |
| Patient's financial cost related to amyloidosis | | | | | | | | |
| Have you had financial costs concerning amyloidosis, i.e. not paid for by public/private healthcare benefits? | 197 (33) | 67 (40) | 46 (37) | 32 (33) | 27 (25) | 13 (50) | 8 (32) | 1 (1) |
| Average cost for the patient during the last 12 months, euros | 656.70 | 800.50 | 509.00 | 528.50 | 814.40 | 366.30 | 694.90 | 676.00 |
| These costs concerned, % (average in euros) | | | | | | | | |
| Transport | 25 (240) | 31 (278) | 27 (164) | 22 (251) | 18 (258) | 40 (348) | 29 (300) | 12 (48) |
| Healthcare worker at home | 16 (98) | 13 (150) | 15 (80) | 20 (76) | 16 (122) | 16 (5) | 25 (78) | 20 (51) |
| Treatment at home | 2 (78) | 4 (23) | 2 (59) | 2 (500) | 0 (0) | 8 (100) | 0 (0) | 4 (1° |
| Physiotherapy | 2 (66) | 5 (56) | 2 (170) | 4 (69) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Psychology | 2 (681) | 4 (830) | 3 (1153) | 0 (0) | 2 (800) | 8 (400) | 0 (0) | 4 (14) |
| Other medical/paramedical consultations | 5 (407) | 8 (571) | 6 (502) | 5 (186) | 2 (800) | 12 (135) | 13 (405) | 8 (99) |
| Impact on professional life | | | | | | | | |
| Yes, during the last 12 months | 20 (11) | 13 (22) | 2 (3) | 3 (10) | 0 (0) | 0 (0) | 1 (11) | 1 (14) |
| Yes, but not during the last 12 months | 19 (11) | 8 (14) | 5 (9) | 4 (13) | 0 (0) | 0 (0) | 1 (11) | 1 (14) |
| Family assistance | | | | | | | | |
| The patient is assisted by a family member? | | | | | | | | |
| Daily | 184 (31) | 50 (29) | 34 (27) | 27 (27) | 45 (41) | 7 (28) | 8 (33) | 13 (25) |
| Occasionally | 96 (16) | 30 (18) | 17 (14) | 22 (22) | 11 (10) | 6 (24) | 4 (17) | 6 (12) |
| Who assists the patient? | | | | | | | | |
| Spouse | 218 (78) | 62 (78) | 38 (75) | 34 (69) | 50 (89) | 9 (69) | 9 (75) | 16 (84) |
| Their child/children | 38 (14) | 12 (15) | 8 (16) | 9 (18) | 5 (9) | 1 (8) | 2 (17) | 1 (5) |
| Another family member | 11 (4) | 3 (4) | 2 (4) | 2 (4) | 1 (2) | 1 (8) | 1 (8) | 1 (5) |
| Repercussions for the family member's work | | | | | | | | |
| Yes, reduced working hours or has stopped work | 8 (3) | 3 (4) | 1 (2) | 1 (2) | 1 (2) | 0 (0) | 1 (8) | 1 (5) |
| Yes, occasionally takes holidays to provide care | 25 (9) | 8 (10) | 8 (16) | 3 (6) | 1 (2) | 2 (15) | 2 (17) | 1 (5) |
| No | 72 (26) | 21 (26) | 14 (27) | 15 (31) | 10 (18) | 3 (23) | 4 (33) | 5 (26) |
| Not applicable (does not work) | 119 (43) | 33 (41) | 21 (41) | 17 (35) | 26 (46) | 8 (62) | 4 (33) | 10 (53) |
| Do not know | 110 (39) | 24 (30) | 25 (49) | 15 (31) | 25 (45) | 7 (54) | 8 (67) | 6 (32) |
| Repercussions for the family member's leisure activities | | | | | | | | |
| Yes | 5 (2) | 3 (4) | 0 (0) | 0 (0) | 1 (2) | 0 (0) | 0 (0) | 1 (5) |
| No | 20 (7) | 8 (10) | 2 (4) | 4 (8) | 4 (7) | 1 (8) | 0 (0) | 1 (5) |

AA: serum amyloid A amyloidosis; AL: immunoglobin light chain amyloidosis; ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis.

### *Delayed diagnosis and the impact on prognosis*

Delays in diagnosis are problematic since they negatively impact prognosis, as well as patient's health and quality of life. Early diagnosis of cardiac amyloidosis is known to confer a better survival prognosis. In recent years, new therapies have been developed that effectively reduced amyloidogenesis [13–19]. Thus, the lengthy process to obtain a confirmed diagnosis means that optimal management of these patients is delayed. Indeed, early treatment of amyloidosis patients may substantially improve survival and quality of life.

### *Disease burden for patients*

At the patient level, our data show that prior to diagnosis amyloidosis is associated with several debilitating symptoms that affect the patients' everyday life. Interestingly, these symptoms are not present to the same extend in the different types of amyloidosis. For example, we observe that more than 70% of patients with ATTRv with cardiomyopathy and ATTRwt have breathlessness, at presentation, whereas breathlessness was reported in at most 25% of patients with ATTRv with neuropathy and other hereditary amyloidosis. Similarly, pain was reported in 36% of patients with ATTRv with neuropathy, 17% with ATTRwt and 44% with AA. Furthermore, 44% of AA patients present with kidney problems, a higher prevalence than that observed in the other types of amyloidosis. This is not surprising since AA is characterised by kidney, gastrointestinal, spleen and liver involvement [20]. Indeed, Papa and Lachmann reported that the vast majority of AA patients present with proteinuria as the first clinical symptom and about half have nephrotic syndrome [21]. The relatively diminished delay in the diagnostic confirmation (19 months) that we observed in AA

patients may be due to the presence of these characteristic symptoms prompting physicians to perform kidney biopsy and allowing for earlier diagnosis. However, even when characteristic symptoms are present in certain types of amyloidosis, diagnosis is complex, and early referral to specialised centres is appropriate when amyloidosis is suspected.

Following diagnosis, patient quality of life deteriorates as amyloidosis progresses. Indeed, most patients reported tiredness, pain and disturbed sleep. Emotionally, most felt angry or anxious, were worried about the future, and felt discouraged. Patients frequently reported that their amyloidosis limited their daily activities. The EQ-5D data suggest that amyloidosis mainly impacts mobility and usual activities, but to a lesser extent selfcare. Furthermore, most patients report pain/discomfort and anxiety/depression. Our results show that amyloidosis not only induces burden at the individual level but also at the family and societal levels.

### *Patients and society*

At baseline, 67% of patients were retired or not working with only 11% forced to stop work. Unfortunately, the survey did not distinguish between patients retired and those not working. When patients completed the survey 30% were working, furthermore, a large proportion of the other patients were retired due to the elderly onset of some types of amyloidosis. Our data concerning the financial impact of amyloidosis must be considered within the context of the French healthcare system. In the French system, the patient's healthcare costs for chronic diseases are completely covered by the national healthcare insurance. Thus, patients with amyloidosis should not have additional costs. However, a third of the patients indicated that they had additional costs, on average 657 euros annually, not covered by the French healthcare assurance and complementary private medical aids. These costs were mainly related to transport and the need for healthcare services at home. About half of patients were assisted daily or occasionally by a family member, predominantly their spouse. It should be noted that 43% of the family members assisting the patients did not work.

### *Limitations of the study*

Due to the rarity of amyloidosis, our study is limited by the number of participants. Nonetheless, this study represents a large population of amyloidosis patient in France. The data collected concerning the financial impact are specific to the French healthcare system and cannot be extrapolate to amyloidosis patients in other countries. Data were collected from amyloidosis patients within a 6-month time interval in 2019. Thus, participating patients were not alike in terms of disease duration and evolution, amyloidosis type and various sociodemographic characteristics. Indeed, we note that overall patients included in the study are younger (mean age) than those treated in real-world clinically situation. Probably, since a higher proportion of elderly and severely ill patients chose not to or were unable to complete the study-specific survey. This heterogeneity induced recall and selection bias in our study. Due to this heterogeneity, no formal comparisons between groups were planned nor performed.

## Conclusion

In conclusion, our data indicate that amyloidosis is a severely debilitating disease for patients physically but also psychologically. Consequently, patients are particularly reliant on their families and support groups. There is a need for increased awareness among the medical community to reduce the time required for a confirmed diagnosis. Today, disease modifying therapies are available for most types of amyloidosis. In addition, these therapies are more efficient if administered early. Patients with suspected amyloidosis should be referred to specialised centres, best equipped to manage these patients, as soon as possible. Furthermore, patients with amyloidosis should receive amyloidosis-specific healthcare at home, including medical, psychological and social care, as well as amyloidosis education. A home-based healthcare programme will reduce patient burden and optimise healthcare in these patients. Most importantly, with recent therapeutic advances, the earlier optimal treatment can be introduced the better the patient outcomes.

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