A Mixed Methods Study of the Journey to Diagnosis Among Patients With Light Chain Amyloidosis

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INTRODUCTION

- Amyloid light chain (AL) amyloidosis is a rare, progressive, and typically fatal disease caused by the deposition of misfolded immunoglobulin light chains, which in turn form soluble toxic aggregates and deposited fibrils (amyloid)[1-3]
  - AL amyloidosis leads to progressive failure of critical organs and systems (eg, heart, kidneys, nervous system), causing significant morbidity and mortality
- Delays in diagnosis are common and may have detrimental consequences on patient prognosis, particularly for patients with cardiac dysfunction
  - Median survival for untreated cardiac patients is approximately 1 year after the onset of symptoms, and it is even lower for those with cardiomyopathy or heart failure[4,5]
- A mixed methods research approach that incorporates both quantitative and qualitative data may provide a more complete understanding of the patient journey to a diagnosis of AL amyloidosis

OBJECTIVES

- To describe the patient journey to diagnosis using a mixed methods research approach
- To examine whether the diagnostic journeys of patients are different for those with and those without cardiac dysfunction

QUALITATIVE STUDY METHODS

Sample and Study Design

- 10 adults (>18 years of age) with self-reported AL amyloidosis were recruited in 2015 with the help of 2 patient advocacy groups (Amyloidosis Support Groups and the Amyloidosis Foundation)
- Individual, 1-hour long interviews were conducted using a semistructured interview guide and a concept elicitation approach

Analysis

- Interviews were audiotaped, transcribed, coded, and analyzed using NVivo software (QSR International, Melbourne, Australia) and a grounded theory approach, which allows themes to emerge from the data rather than imposing a priori hypotheses to be tested[6]
  - Dual coding and review meetings ensured agreement among 4 coders
  - Analysis of saturation was conducted to ensure that enough interviews had been conducted to allow full understanding of the concepts that emerged

QUANTITATIVE STUDY METHODS

Sample and Study Design

- Adults with self-reported AL amyloidosis were recruited to participate in a longitudinal, observational, online study
- Amyloidosis Support Groups and the Amyloidosis Foundation also helped to support recruitment efforts, which consisted of social media posts and emails announcing the opportunity for study participation
- Patients completed an initial survey (N = 341) to assess patient characteristics and diagnostic history. A subset of patients (n = 185) completed an 18-month follow-up survey and reported whether specific types of diagnostic procedures were performed before their diagnosis

Statistical Analysis

- Descriptive statistics were used to summarize the diagnostic journey in terms of
  - Time between symptom onset and diagnosis
  - Number of doctors and specialty types seen before diagnosis
  - Number and types of diagnostic procedures before diagnosis
- Patients were categorized according to
  - Cardiac dysfunction (yes/no)
  - Early diagnosis (<6 months from symptom onset) or delayed diagnosis (≥6 months from symptom onset)
- Chi-square tests were used to examine differences in the journey to diagnosis by cardiac dysfunction
- Log binomial models were used to estimate the relative risk (RR) associated with delayed diagnosis for specific types of primary organ dysfunction

RESULTS

Sample Characteristics

- An overview of the characteristics of the qualitative and quantitative samples is provided in **Table 1**

Table 1. Demographic and Disease Characteristics for Qualitative and Quantitative Study Samples

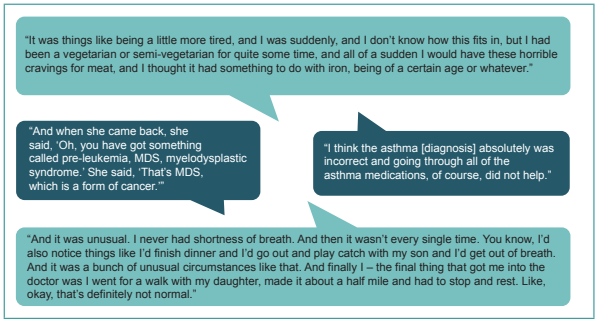
	Qualitative Sample N = 10 n (%)	Quantitative Sample N = 341 n (%)
Age, years		
Mean (range)	57 (41-76)	60 (23-85)
Gender[a]		
Female	6 (60.0)	180 (52.9)
Male	4 (40.0)	160 (47.1)
Highest level of education completed[a]		
<4-year college degree	4 (40.0)	125 (38.8)
College degree (BA, BS)	3 (30.0)	109 (33.9)
Advanced degree (MA, PhD, MD)	3 (30.0)	88 (27.3)
Region (in US)		
Northeast	2 (20.0)	68 (20.0)
Midwest	3 (30.0)	54 (15.9)
South	4 (40.0)	79 (23.2)
West	1 (10.0)	81 (23.8)
Other (including international)	0 (0.0)	58 (17.1)
Time since diagnosis, years		
Mean (range)	2.1 (3 months-8 years)	4.5 (1 month-28 years)
Organ/system affected by AL amyloidosis[b]		
Heart	6 (60.0)	178 (52.2)
Kidney	4 (40.0)	214 (62.8)
Gastrointestinal	3 (30.0)	148 (43.4)
Nervous	2 (20.0)	126 (37.0)
No. of organs affected		
1	5 (50.0)	95 (27.9)
≥2	5 (50.0)	246 (72.1)
Hematologic response to treatment (remission status)		
Complete hematologic response	5 (50.0)	141 (41.3)
Partial hematologic response	1 (10.0)	126 (37.0)
No response/disease progressing	4 (40.0)	23 (6.7)
Do not know	0 (0.0)	51 (15.0)

[a]Frequencies less than the total sample size are due to missing data; percentages are based on available data.
[b]Only the 4 most commonly reported organs or systems are included in the table; multiple options were allowed.

Qualitative Findings: Barriers to Early Diagnosis

- During the in-depth interviews, all patients reported ≥1 barrier to diagnosis, such as not promptly seeking medical help because of the interpretation of their initial symptoms or because of the challenging differential diagnostic process, which included multiple doctors, multiple diagnostic procedures, and/or frequent misdiagnoses
  - The mean duration of time between experiencing initial symptoms and receiving a diagnosis of AL amyloidosis was 2 years (range, 3 months-4 years)
  - For 3 of 10 patients, a single event, such as an abnormal result from a routine test (eg, urinalysis), was the first indicator that they were ill. Other patients noticed worrisome symptoms on their own and sought medical help
  - Patients reported experiencing a variety of initial symptoms, many of which mimicked those of other more prevalent diseases. The misattribution of these symptoms by both patients and clinicians might have contributed to delays in diagnosis
  - Patients reported seeing, on average, 3 different types of specialists before receiving a correct diagnosis
  - 8 of 10 patients initially received a misdiagnosis
- Patients described some of the barriers they experienced in seeking an accurate diagnosis (**Figure 1**)

Figure 1. Challenges experienced in pursuit of a diagnosis: results from qualitative interviews.

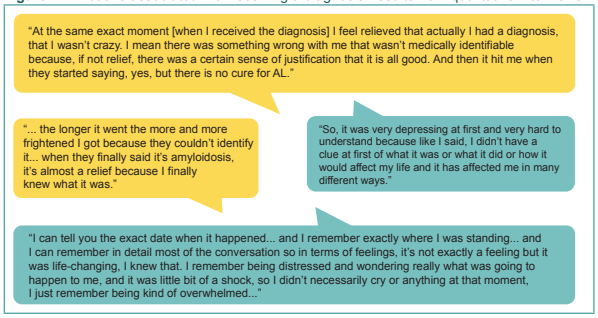


Quotations against a dark teal background are examples of misdiagnoses. Quotations against a light teal background are examples of nonspecific symptoms experienced by patients; in some cases, nonspecific symptoms were misattributed to other causes, delaying accurate diagnosis.

Qualitative Findings: Emotional Toll of the Journey

- Although some patients reported feeling relieved to finally have an accurate diagnosis (n = 3), most patients discussed feeling overwhelmed and worried about the seriousness of the disease (n = 8)
- Patients described the emotions they experienced when learning of their diagnosis (**Figure 2**)

Figure 2. Emotions associated with receiving a diagnosis: results from qualitative interviews.



Quotations against a yellow background are examples of the feelings of relief that sometimes accompanied an accurate diagnosis. Quotations against a light teal background are examples of the negative emotions that accompanied the diagnosis.

Quantitative Findings: Summary of the Journey to Diagnosis

- As shown in **Table 2**, time to diagnosis varied across the surveyed patients, with 43% of the sample reporting that it took ≥1 year to receive a diagnosis after they began experiencing symptoms
- Similar to that seen in the qualitative findings, surveyed patients reported seeing multiple doctors and different types of specialists as they sought an accurate diagnosis
- Patients with cardiac dysfunction saw more doctors and underwent more diagnostic procedures before the diagnosis than patients without cardiac dysfunction ($P < 0.05$ for both)

Table 2. Journey to Diagnosis Based on Cardiac Dysfunction: Results From the Quantitative Survey

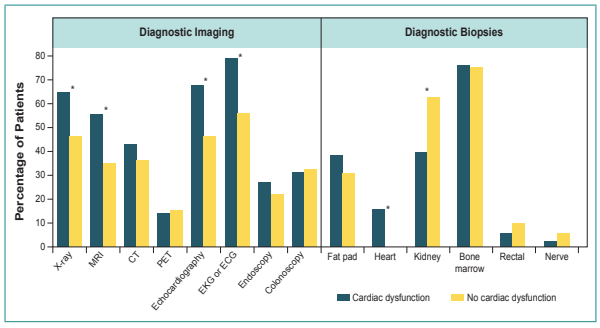
	All Surveyed Patients N = 341 n (%)	Cardiac Dysfunction		*P*
		Yes n = 178 n (%)	No n = 163 n (%)	
Time between onset of symptoms and diagnosis				0.426
<6 months	96 (28.2)	45 (25.3)	51 (31.3)	
≥6-<12 months	97 (28.5)	51 (28.7)	46 (28.3)	
≥12 months	148 (43.4)	82 (46.1)	66 (40.5)	
No. of doctors seen before diagnosis				0.005
1-2	68 (20.0)	26 (14.6)	42 (25.8)	
3-4	128 (37.5)	63 (35.4)	65 (40.0)	
≥6	145 (42.5)	89 (50.0)	56 (34.4)	
No. of specialty types before diagnosis				0.063
1-2	91 (26.7)	39 (21.9)	52 (31.9)	
3-4	155 (45.5)	82 (46.1)	73 (44.8)	
≥6	95 (27.9)	57 (32.0)	38 (23.3)	
No. of diagnostic procedures before diagnosis[a]				0.048
1-4	38 (20.7)	13 (14.4)	25 (26.6)	
5-7	52 (28.3)	22 (24.4)	30 (31.9)	
8-9	55 (29.9)	31 (34.4)	24 (25.5)	
≥10	39 (21.2)	24 (26.7)	15 (16.0)	

[a]Numbers and types of diagnostic procedures were assessed among a subset of patients who completed the 18-month follow-up survey (n = 185).

Quantitative Findings: Diagnostic Testing

- On average, patients reported undergoing 7 types of diagnostic procedures, including an average of 2 biopsies. The most common diagnostic procedures were blood tests (97%), urinalysis (89%), bone marrow biopsy (75%), and electrocardiography (67%)
- As depicted in **Figure 3**, imaging tests (eg, X-ray, magnetic resonance imaging) were more common among patients with cardiac dysfunction than without cardiac dysfunction

Figure 3. Percentage of patients with and without cardiac dysfunction who underwent specific diagnostic tests (n = 185).



*$P < 0.05$.

Quantitative Findings: Characteristics Associated With Delayed Diagnosis

- Patients who identified the heart as their most affected organ were 43% more likely to experience delayed diagnosis than patients who identified the kidney as their most affected organ (RR, 1.43; 95% confidence interval, 1.21-1.69)

CONCLUSIONS/SUMMARY

- During qualitative interviews, patients described a complex journey to diagnosis that included consultations with multiple doctors, a variety of diagnostic procedures, and frequent misdiagnoses
- The quantitative data complement and extend these findings, elucidating the ways in which patients' journeys may vary based on specific types of organ dysfunction (eg, cardiac), particularly in terms of number of doctors seen, number of diagnostic procedures experienced, and time to diagnosis
- The emotional toll and frustration caused by rounds of testing and visits to specialists suggest the need for improvements toward early diagnosis, better approaches to diagnostic testing, and increased clinician awareness, particularly for patients with cardiac dysfunction
- Barriers to early diagnosis not only delay treatment but may impair the patient-physician relationship and increase health care resource utilization and costs
- Examination of additional risk factors associated with diagnostic delays, such as specific symptom profiles, disease characteristics, and patterns of health care utilization, is warranted

REFERENCES

1. Merlini G, Bellotti V. *N Engl J Med.* 2003;349:583-596.
2. Sanchorawala V. *Clin J Am Soc Nephrol.* 2006;1:1331-1341.
3. Mahmood S et al. *Haematologica.* 2014;99:209-221.
4. Dubrey SW et al. *QJM.* 1998;91:141-157.
5. Falk RH et al M. *N Engl J Med.* 1997;337:898-909.
6. Strauss AL, Corbin JM. *Basics of Qualitative Research: Grounded Theory Procedures and Techniques.* Newbury Park, CA; 1990.

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