

The Impact of Hereditary Transthyretin Amyloidosis on Work-Related Outcomes: A Mixed Methods Approach

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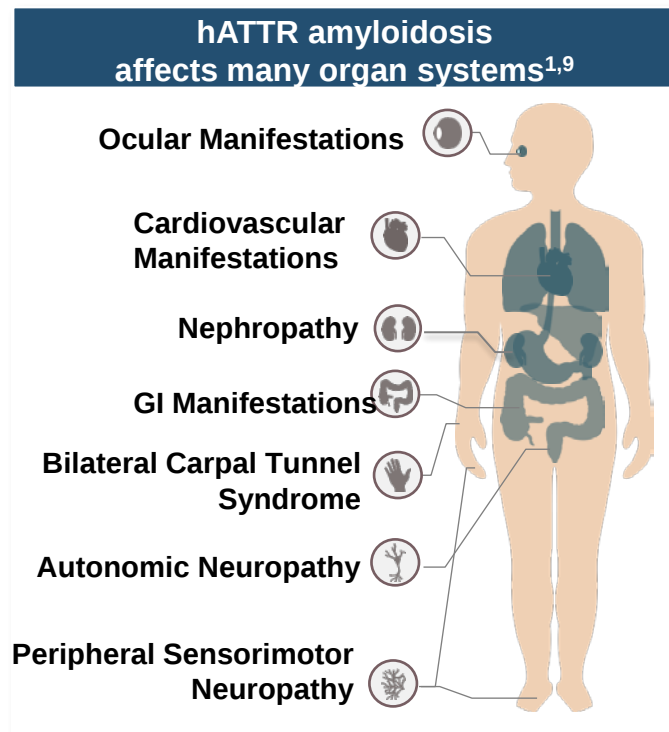


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Background: hATTR Amyloidosis

- Hereditary transthyretin (hATTR) amyloidosis is a rare, progressive, and fatal disease that results from buildup of misfolded transthyretin proteins in major organs and organ systems^{1,2}
- Patients typically live 3-15 years after diagnosis,³ but patients with cardiac involvement only live 2-6 years⁴
- Patients experience significant disease burden, morbidity, and a rapid decline in quality of life; symptoms impact multiple aspects of daily life⁵⁻⁸



1. Conceição I et al. *J Peripher Nerv Syst.* 2016;21:5-9; 2. Ando Y et al. *Orphanet J Rare Dis.* 2013;8:31; 3. Gertz MA. *Am J Manag Care.* 2017;23:S107-S112. 4. Maurer et al. *Circulation.* 2017;135:1357–1377. 5. Coelho T et al. *Muscle Nerve.* 2017;55(3):323-332; 6. Adams D et al. *Orphanet J Rare Dis.* 2015;10(suppl 1):P58. 7. Amyloidosis Foundation. Understanding the patient voice in hereditary transthyretin-mediated amyloidosis (ATTR amyloidosis). http://www.amyloidosisissupport.org/support_groups/fam_isabell_attr.pdf. Accessed November 15, 2018; 8. Stewart M et al. *Neurol Ther.* 2018; 9. Sperry B et al. *J Am Coll Cardiol.* 2018;72:2040-50.

Study Design and Objective

- A mixed methods embedded design was used to examine the impact of hATTR amyloidosis on adults in the US and Canada, specifically patients' work-related outcomes through qualitative interviews and observational survey data
- Qualitative data were based on 14 concept elicitation interviews with patients
 - 11 patients reported that they were in the workforce at symptom onset, while 3 had retired prior to symptom onset
- Quantitative data were based on 57 surveys completed by patients collected in an observational, online study
 - 42 patients reported that they were in the workforce at symptom onset, while 15 had retired or exited the workforce prior to symptom onset

Qualitative Methods

- 14 one-on-one, 70-minute, in-depth, interviews were conducted in April/May, 2018
- Recruitment: Boston University's Amyloidosis Center and the Amyloidosis Support Groups (ASG)
- Interviews were conducted in person (n=2) or by phone (n=12) using concept elicitation techniques and a semi-structured interview guide
 - Open-ended, exploratory questions allowed for spontaneous responses and rich descriptions of patient experiences; with follow-up probes used, as needed, to refine and clarify details of the information gathered
- Transcripts were content coded using NVivo qualitative research software and grounded theory analysis methods¹⁰
- Saturation, where no new important and relevant codes emerged, was assessed by comparing codes in consecutive sets of interviews

10. Strauss A, Corbin J. Basics of Qualitative Research: Techniques and Procedures for Developing Grounded Theory. London: Sage; 1998

Quantitative Methods

- 94 surveys from adult patients in the US and Canada with self-reported ATTR amyloidosis enrolled in an online, longitudinal observational survey study between July 2018 and April 2019
 - 57 surveys from patients with hATTR amyloidosis were used in this analysis
- Recruitment:
 - Patient advocacy groups (ASG, Amyloidosis Foundation, Amyloidosis Research Consortium)
 - An online health management portal (BackpackHealth.com)
 - Akcea's medical science liaisons
- Work-related data was collected on employment history, current employment, and work productivity, as measured by Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI: SHP)
- Survey item responses and WPAI scores were summarized descriptively

Sample Characteristics

Characteristic	Qualitative Sample (n = 14)	Quantitative Sample (n = 57)
Demographics		
Age [Years], Mean $\pm$ SD (range)	61.5 $\pm$ 14.5 (20 – 76)	61.7 $\pm$ 10.5 (37 – 78)
Male, n (%)	8 (57%)	30 (53%)
Caucasian/White, n (%)	13 (93%)	44 (77%)
Bachelor's degree or higher, n (%)	11 (79%)	41 (72%)
Employment status (full or part-time), n (%)		
At symptom onset	11 (79%)	42 (74%)
Current (at time of interview/survey)	3 (21%)	18 (32%)
Married, n (%)	10 (71%)	43 (75%)
Region [Canada], n (%)	1 (7%)	3 (5%)

Disease and Treatment History

Characteristic	Qualitative Sample (n = 14)	Quantitative Sample (n = 57)
Disease Onset and Diagnosis		
Age [Years], Mean ± SD (range)		
At first hATTR symptom	50.4 ± 15.1 (14 – 73)	53.8 ± 1.5 (28 – 75)
At diagnosis	56.3 ± 16.6 (17 – 75)	55.5 ± 1.7 (18 – 76)
Number of years, Mean ± SD (range)		
Since symptom onset	11.1 ± 9.6 (3 – 36)	8.3 ± 6.1 (1 – 30)
Since diagnosis	5.2 ± 5.6 (1 – 21)	2.8 ± 5.1 (0 – 27)
Current hATTR Treatment*, n (%)		
Diflunisal	6 (43%)	22 (39%)
Doxycycline + tauroursodeoxycholic acid (TUDCA)	1 (7%)	5 (9%)
Inotersen	0 (0%)	9 (16%)
Patisiran (Onpattro)	5 (36%)	13 (23%)
Not currently on hATTR treatment**	5 (36%)	17 (30%)
Past Surgical Treatment*, n (%)		
Organ transplant (e.g. liver)	2 (14%)	6 (11%)
Other Surgery (e.g. Carpal tunnel surgery)	3 (21%)	26 (46%)
Ambulatory Disability Stage*, n (%)		
Stage 1 - Does not require assistance with walking	7 (50%)	41 (72%)
Stage 2 - Requires assistance with walking	4 (29%)	12 (21%)
Stage 3 - Unable to walk	3 (21%)	4 (7%)

* Percentage may sum to more than 100%; patients were allowed to report more than one treatment

** Patients may have reported treatments designed to alleviate specific symptoms, but not ATTR amyloidosis

SD: Standard Deviation

Disease-related Healthcare Resource Utilization and Symptoms Lead to Absenteeism

Qualitative Sample

One-third (n=4, 36%) reported missing work due to their hATTR amyloidosis-related for:

- Healthcare appointments, diagnostic/clinical tests, and treatment visits
- Symptoms, including pain (n=3) and gastrointestinal dysfunction (n=2)

Quantitative Sample

Employed patients reported missing an average **4.9 hours of work** in the past week, or 12% of their work week, due to hATTR amyloidosis

“But then—then my symptoms started to get worse. I would have to call out pretty often. There were some days, I was in so much pain, that just standing would make me cry.”

[08 – Female, Age 20]

Disease Symptoms and Treatment Side Effects Lead to Impairments at Work (Presenteeism)

Qualitative Sample

- **64% (n=7) of patients attributed work impairments to ATTR amyloidosis symptoms or symptom impacts**
 - Difficulty gripping/holding (n=3), cognitive difficulties (n=3), pain (n=2), fatigue (n=2), and GI dysfunction (n=2)
- **18% (n=2) reported work impairments due to treatment side effects**
 - Fatigue, trouble focusing, difficulty finding words, memory issues, and “feeling loopy”

Quantitative Sample

- The average percentage of impairment while at work was 25% among employed patients (WPAI – presenteeism)
- The percentage of overall productivity loss (absenteeism and presenteeism) was 30% (WPAI)

**Difficulty
Gripping/
Holding**

“I find it more difficult holding the hammer, using the hammer, [...] I have air hammers and such but even holding that big gun and, you know, a finish gun I can hold in my hand that it's light but if I have to hold up the framing gun like I did a couple days ago—anything that gets up over my shoulders, [it's difficult]. Even, this is odd, but if I put my hands on the top of the steering wheel on the tractor or in the truck, my hands get numb.”

[12 – Male, Age 66]

**GI
Dysfunction**

“Oh irritable bowels. Does anybody know that I have that? If I say I have to go, in meetings or I just pick up and I go.”

[05 – Female, Age 52]

**Trouble
Focusing**

“In my job, I'm the [one who is] responsible, so I'm leading the meetings, I'm making sure that everything stays on track and everything's managed the way it's supposed to be. So I definitely had concerns over being able to be my best at that like I normally was. Which just impacts everything, because then you feel like you're not doing your job the best you could be, or you're a little scattered. You get disorganized, and then, that has a big downstream impact.”

[02 - Female, Age 48]

Symptom and Treatment Burden Lead to Employment Transitions

Qualitative Sample

About three-quarters (n=8, 73%) of patients reported leaving the workforce or switching jobs due to symptom or treatment burden

The most common symptom impact leading to leaving the workforce was **difficulty walking or standing** (n=5, 45%)

Quantitative Sample

About half (n=30, 53%) of patients reported they changed, reduced, or left their jobs to reduce their work burden or to accommodate their care

The most common transitions in employment status were out of employment into retirement (n=11, 41%) and disability (n=9, 33%)

“So, I started working in a leadership position with this new company, and I was only with them for 13 months when I had to say that was it. I could not work. So, I went from being fully capable to having to hide because of this disability.”

[03 – Male, Age 65]

“I was an executive at a large multi-office architecture company. And so by the time I was in a position, physically, to go back to work, well, they couldn’t wait for me...so once I had my transplants and I recovered enough to be able to go back to work, my old job was no longer available to me.”

[10 – Female, Age 66]

Prematurely Exiting the Workforce May Be Detrimental to Patient Well-being

Qualitative Sample

- Patients reported a desire to continue working as their hATTR amyloidosis progressed
- Patient well-being decreased due to premature workforce exits

“Well, losing my hand function was a big turning point, because that kind of spelled the end of my career. I had to stop working. [...] Although, I mean, you know when I was first diagnosed I kept working. I wasn't ready to retire just yet, so I kept working, even with the pain of polyneuropathy, and you know, the reducing function in my lower extremities. As long as I was still walking, I'm still able to use my hands, I was able to work. But when that went, that was that and I had to stop [...] That was horrible. I had a good career going, a good income coming in, and that was a big life change. That's a big left turn in how things were going. I wasn't ready to retire. I didn't want to retire. And certainly not because of medical reasons. But I got to the point where I didn't have a choice. It was what it was, and it was time for me to stop.”

[07 – Male, Age 57]

Summary

- Patients with hATTR amyloidosis experienced disruptions in their ability to go to work and be productive while at work
 - Led by symptoms such as pain, fatigue, and decreased mobility
- The majority of patients prematurely exited the workforce due to the symptoms of hATTR amyloidosis or its treatment burden
- Patients who prematurely exited the workforce were negatively impacted psychologically and would have preferred to keep working

Study Limitations

- Due to concurrent study fielding, results from one study did not inform the other
- The study enrolled few patients (n=4) with only symptoms of cardiomyopathy in the observational survey only
- Findings may not reflect the work-related impacts of the disease for patients with earlier symptom onset
 - Average age at symptom onset in both samples was around 50 years old, resulting in a sample that was primarily retired or close to retirement at data collection

Study Strengths

- Mixed methods design allowed survey data from a patient sample with a rare condition to be complemented with in-depth narrative data from qualitative interviews, providing context on how hATTR amyloidosis impacts patient ability to work
 - Overlapping study team members designed the interview guides and survey to capture data on cross-cutting themes
 - Findings were consistent across study samples
- Provides rich data, in the patients' own voice, on the impact of hATTR amyloidosis on work productivity, symptom and treatment burden on employment, and employment transitions

Conclusions and Implications

- This study found:
 - Patients with hATTR amyloidosis experienced high levels of employment interference and disruption
 - Symptoms and treatment burden of hATTR amyloidosis led to early transitions out of the workforce and serious negative impacts on patients' overall independence and emotional well-being
- This highlights the need for effective treatments that reduce symptom and treatment burden while allowing patients to remain in the workforce longer

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Sample Disease Characteristics

Characteristic	Qualitative Sample (n = 14)	Quantitative Sample (n = 57)
hATTR Phenotype, n (%)		
Symptoms of polyneuropathy only	6 (43%)	26 (46%)
Symptoms of cardiomyopathy only	0 (0%)	4 (7%)
Symptoms of both polyneuropathy and cardiomyopathy	8 (57%)	27 (47%)
hATTR Genetic Variant, n (%)		
Thr60Ala	3 (21%)	18 (32%)
Val30Met	5 (36%)	10 (18%)
Val122Ile	0 (0%)	8 (14%)
Other	4 (29%)	18 (32%)
I don't know/don't remember	2 (14%)	3 (5%)
Ambulatory Disability Stage*, n (%)		
Stage 1 - Does not require assistance with walking	7 (50%)	41 (72%)
Stage 2 - Requires assistance with walking	4 (29%)	12 (21%)
Stage 3 - Unable to walk	3 (21%)	4 (7%)
Organ/System Involved**, n (%)		
Cardiac	14 (100%)	34 (60%)
Nervous system (peripheral/autonomic neuropathy)	6 (43%)	49 (86%)
Gastrointestinal	6 (43%)	26 (46%)
Ocular	3 (21%)	14 (25%)
Kidney	0 (0%)	8 (14%)

* Coutinho P, Martins da Silva, A., Lopes Lima J, et al. Forty years of experience with type 1 amyloid neuropathy. Review of 483 cases. In: Glenner G, Costa P, Freitas A de, eds. Amyloid and Amyloidosis. Amsterdam: Excerpta Medica; 1980:88–98.

** Percentage may sum to more than 100%; participants were allowed to selected more than one response option