The Journey to Diagnosis of ATTR Amyloidosis: Burden of Early Disease

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Conclusions

- **Patients with transthyretin-mediated (ATTR) amyloidosis experience a myriad of burdensome symptoms and other diagnoses on their journey to ATTR amyloidosis diagnosis**
- **Symptoms may start more than 10 years before diagnosis and appear to accumulate over time**
- **Neuropathy- and cardiovascular (CV)-related symptoms are reported in both hereditary ATTR (hATTR) and wild-type ATTR (wtATTR) amyloidosis in the 10 years pre-diagnosis, highlighting the multisystem nature of ATTR amyloidosis**
- **These results suggest that clinicians should implement specific strategies to facilitate earlier diagnosis of ATTR amyloidosis such as:**
  - **Using electronic medical record-embedded screening tools to support earlier detection of non-specific symptomatology**
  - **Critical evaluation of a patient's full medical history**

Introduction

ATTR Amyloidosis

- An underdiagnosed, progressive, debilitating, and fatal disease caused by misfolded transthyretin (TTR) protein accumulating as amyloid deposits in multiple organs and tissues including the nerves, heart, gastrointestinal tract, and musculoskeletal tissues[1–14]
- ATTR amyloidosis is classified as hereditary (hATTR amyloidosis), caused by pathogenic *TTR* gene variants, or wild-type (wtATTR amyloidosis), with no variant present[1]
- Multisystem involvement including cardiac, sensory, motor, and autonomic neuropathy, as well as soft tissue/orthopedic manifestations, has been seen in both types of ATTR amyloidosis[1–14]
  - This heterogenous, non-specific symptomology contributes to diagnostic delays of up to several years, frequently reported for this disease[15–17]

Objective

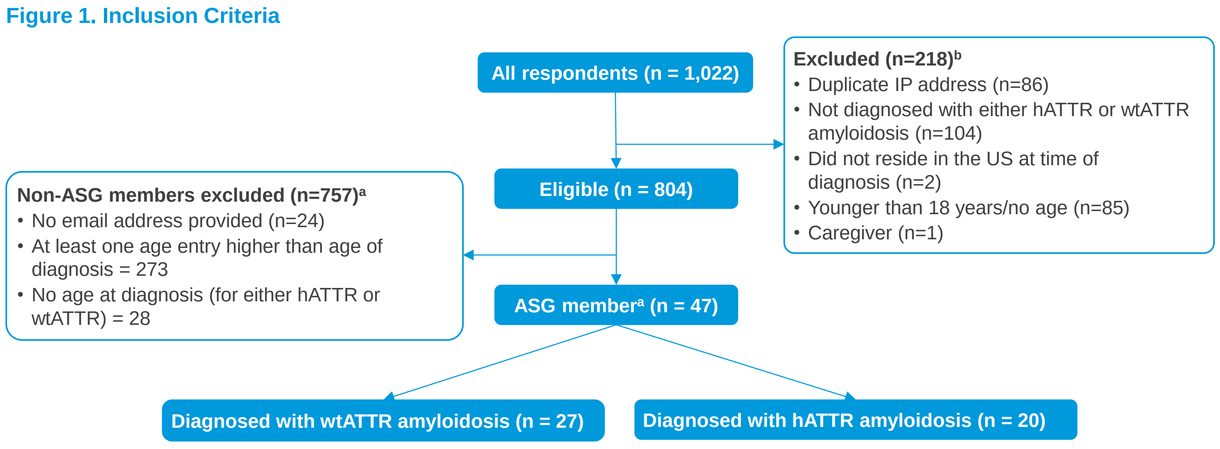
- To gain insights on patients' medical histories and the burden of symptoms possibly related to the disease on their path to ATTR amyloidosis diagnosis using a patient survey

Methods

Online Patient Survey

- An online patient-reported survey was conducted in 2020 in collaboration with Amyloidosis Support Groups (ASGs) to understand patients' physical and medical experiences before diagnosis of hATTR or wtATTR amyloidosis
- Subjects were required to be US residents, ≥18 years old, ASG members, and have an ATTR amyloidosis diagnosis for inclusion in this analysis (**Figure 1**)
- Patients reported signs/symptoms, diagnoses, and procedures prior to ATTR amyloidosis diagnosis which were summarized at >10, 4–10, and <4 years pre-ATTR amyloidosis diagnosis
  - Symptoms, diagnoses, and procedures were categorized post hoc as neuropathy related, CV related, or orthopedic related (diagnosis and procedures only) in consultation with expert physician advisors

Figure 1. Inclusion Criteria



[a]Subjects were ASG members at the time of the online survey (not at diagnosis). [b]Respondents may be excluded for more than one reason so sum of individual exclusion criteria does not equate to total n of excluded respondents

Results

Patient Demographics and Characteristics (Table 1)

- Patients with hATTR amyloidosis (n=20) had a lower mean age at diagnosis (60.1 years) than patients with wtATTR amyloidosis (69.9 years, n=27)
- The majority of patients with hATTR amyloidosis were female (55%) whereas most patients with wtATTR amyloidosis were male (89%)
- The majority of patients included in the analysis were White (85%)
- 26% and 35% of patients with wtATTR and hATTR amyloidosis, respectively, had a mixed phenotype of both polyneuropathy and cardiomyopathy

Table 1. Baseline Characteristics

Demographics and Characteristics	Subjects with wtATTR Amyloidosis (n = 27)[a]	Subjects with hATTR Amyloidosis (n = 20)[b]
Current age, years, mean	72.5	65.6
Age at diagnosis, years, mean (range)	69.9 (46–82)	60.1 (42–79)
Years since diagnosis, mean (range)	2.6 (0–11)	5.5 (0–26)
Male gender, n (%)	24 (89)	9 (45)
Ethnic background, n (%)		
White	23 (85)	17 (85)
Asian	1 (4)	1 (5)
Black or African American	2 (7)	2 (10)
Other	1 (4)[c]	0
Diagnoses of polyneuropathy and/or cardiomyopathy, n (%)		
Cardiomyopathy	17 (63)	3 (15)
Polyneuropathy	1 (4)	9 (45)
Both polyneuropathy and cardiomyopathy	7 (26)	7 (35)
I don't know/neither/blank	2 (7)	1 (5)
Diagnosing physician, n (%)		
Primary care physician	0	3 (15)
Neurologist	0	4 (20)
Cardiologist	23 (85)[d]	8 (40)
Hematologist	1 (4)	2 (10)
I don't know	0	1 (5)
Other	3 (11)	2 (10)

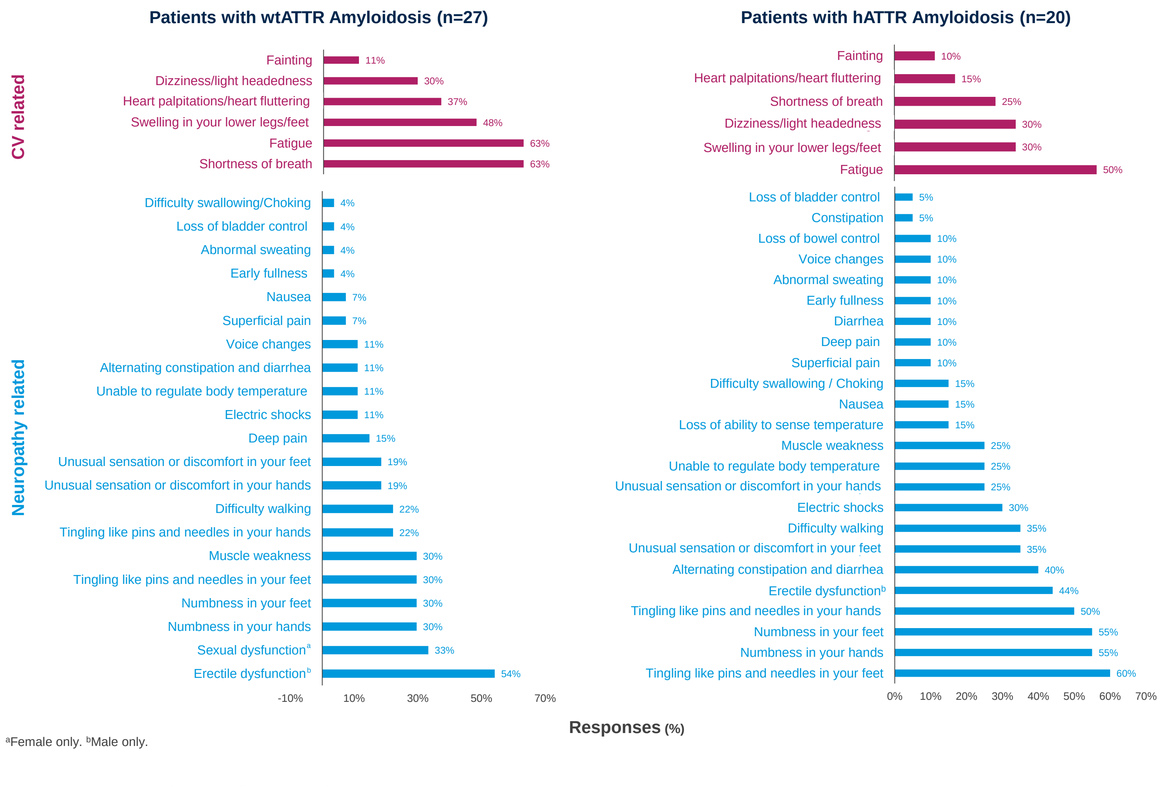
[a]Two patients self-reported a wtATTR amyloidosis diagnosis but had missing genetic test data. [b]TTR variants included T60A (n=8), V122I (n=1), V30M (n=5), L58H (n=2), F64L (n=1), A117S (n=1), E54Q (n=1), and P597Y (n=1) as reported by subjects. [c]One participant responded 'American'. [d]One participant specified their diagnosis was advanced heart failure diagnosed by a cardiologist.

Most Commonly Reported Signs/Symptoms

- A substantial symptom burden was reported pre-diagnosis, with 55% of patients with hATTR amyloidosis and 19% of patients with wtATTR amyloidosis reporting ≥7 disease-typical signs/symptoms
- Prior to diagnosis, patients reported both CV- and neuropathy-related signs/symptoms (**Figure 2**)
- In hATTR amyloidosis, neuropathy signs/symptoms were most commonly reported, including tingling in feet (60%), numbness in hands (55%), and numbness in feet (55%), although CV signs/symptoms were also present (fatigue, swelling in lower legs/feet, and dizziness/light headedness)
- In wtATTR amyloidosis, CV signs/symptoms were most commonly reported, including fatigue (63%) and shortness of breath (63%), although neuropathy signs/symptoms were also present (numbness in hands/feet, tingling-like pins and needles in your feet, muscle weakness)

Results (cont.)

Figure 2. Prevalence of Pre-Diagnosis CV- and Neuropathy-Related Signs/Symptoms



[a]Female only. [b]Male only.

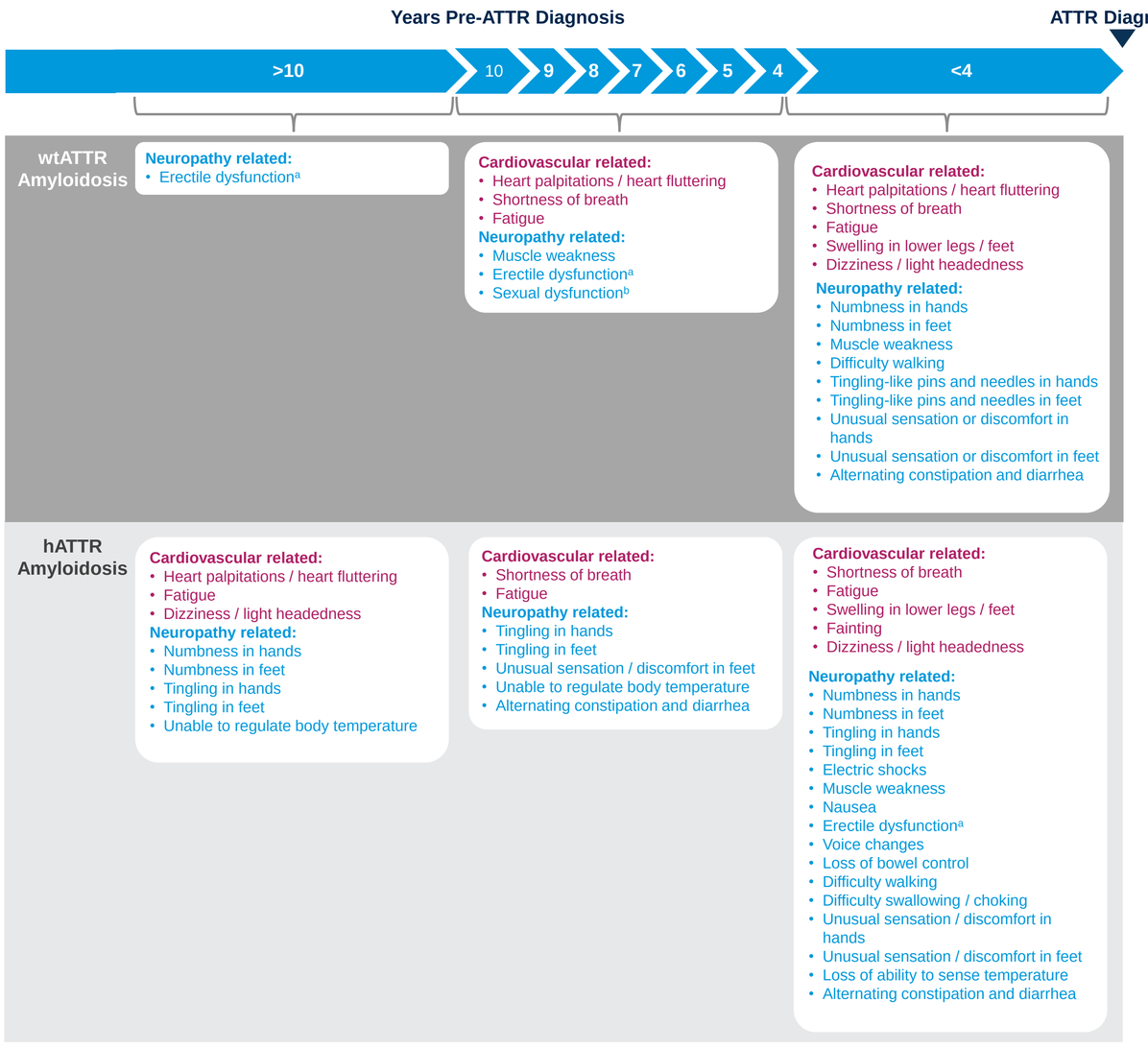
Burden of Pre-Diagnosis Signs/Symptoms

- Both neuropathy- and CV-related signs/symptoms with a severe/very severe impact on daily life occurring before diagnosis of ATTR amyloidosis were reported
  - Patients with hATTR amyloidosis reported a greater range of neuropathy-related signs/symptoms with a severe/very severe impact on daily life than patients with wtATTR amyloidosis
  - A greater proportion of patients with wtATTR amyloidosis reported a severe/very severe impact of shortness of breath than patients with hATTR amyloidosis
  - For patients with hATTR or wtATTR amyloidosis, the autonomic neuropathy-related symptom of erectile dysfunction and neuropathy-related symptom of walking difficulty were among those which were most frequently considered to have a severe/very severe impact on daily life

Timing of Signs/Symptoms Prior to ATTR Amyloidosis Diagnosis

- Signs/symptoms were reported >10 years pre-diagnosis in both disease types; however, the mix of signs/symptoms differed (**Figure 3**)
  - In patients with hATTR amyloidosis, both neuropathy and CV signs/symptoms were reported in ≥10% of patients at >10 years pre-diagnosis, and persisted up to diagnosis
  - In patients with wtATTR amyloidosis, one symptom, erectile dysfunction, potentially related to autonomic neuropathy in ≥10% of (male only) patients was reported at >10 years pre-diagnosis; CV and other neuropathy signs/symptoms became more frequently reported <10 years pre-diagnosis
- The number of signs/symptoms reported by ≥10% of patients markedly increased as patients approached diagnosis of ATTR amyloidosis
- In both disease types, some of the earliest neuropathy and CV signs/symptoms were reported to have moderate/severe impacts on daily life

Figure 3. Occurrence of Signs/Symptoms in ≥10% of Patients Prior to ATTR Amyloidosis Diagnosis



[a]Male only. [b]Female only.

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