The Journey to Diagnosis of Wild-Type ATTR Amyloidosis: A Path with Multisystem Involvement

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Introduction

Wild-Type Transthyretin-Mediated (wtATTR) Amyloidosis

- A non-hereditary, progressive, debilitating, and fatal disease caused by the accumulation of amyloid fibrils, consisting of wild-type (wt) transthyretin (TTR)[1–5]
- Disease typically occurs in older individuals, and is more common in men, but recent studies suggest a substantial proportion of women are also affected[6–8]
- Cardiomyopathy is usually the most common presentation at diagnosis, with approximately 90% of patients with wtATTR amyloidosis reporting heart failure[3]
- However, wtATTR amyloidosis is a multisystem disease that can also include sensory, motor, and autonomic neuropathy, and soft-tissue/orthopedic manifestations[1–4,9–15]
- While patients are often diagnosed upon presentation with cardiovascular (CV) symptoms, recent data suggest extra-cardiac systems are impacted earlier in the disease course[7,9,11]

Hypothesis

- wtATTR amyloidosis manifests years prior to diagnosis of cardiomyopathy, with multisystem involvement that includes neurologic, soft-tissue/orthopedic, and CV signs/symptoms

Abbreviations: CV, cardiovascular; TTR, transthyretin; wt, wild-type; wtATTR, wild-type transthyretin-mediated.

References: 1. Hawkins et al. *Ann Med* 2015;47:625–38; 2. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92; 3. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 4. Živković et al. *Amyloid* 2020;27:142–3; 5. Sipe et al. *Amyloid* 2014;21:221–4; 6. Rapezzi et al. *Nat Rev Cardiol* 2010;7:398–408; 7. Lane et al. *Circulation* 2019;140:16–26; 8. Gonzalez-Lopez et al. *Eur Heart J* 2017;38:1895–904; 9. M'bappe et al. *Best Pract Res Clin Rheumatol* 2012;26:459–75; 10. Aus dem Siepen et al. *Clin Res Cardiol* 2019;108:1324–30; 11. Gorevic ISA Congress 2020. Poster PT135; 12. Milandri et al. *Eur J Heart Fail* 2020;22:507–15; 13. Campbell et al. ISA Congress 2020. Poster PT119; 14. Nakagawa et al. *Amyloid* 2016;23:58–63; 15. Sueyoshi et al. *Hum Pathol* 2011;42:1259–64.

Methods

Online Patient Survey

- An online patient-reported survey was conducted in 2020 in collaboration with Amyloidosis Support Groups (ASG), a US-based non-profit that starts and maintains amyloidosis support groups, to understand patients' physical and medical experiences before ATTR amyloidosis diagnosis (wtATTR or hereditary transthyretin-mediated [hATTR] amyloidosis)
- Subjects were required to be US residents, ≥18 years old, ASG members, and have a wtATTR amyloidosis diagnosis for inclusion in the analysis
- Patients reported symptoms, diagnoses, and procedures prior to wtATTR amyloidosis diagnosis, which were summarized at >10, 4–10, and <4 years pre-wtATTR amyloidosis diagnosis
  - Symptoms, diagnoses, and procedures were defined as neuropathy related, CV related, or orthopedic related (diagnosis and procedures only) by the clinical consultants

Abbreviations: ASG, Amyloidosis Support Groups; ATTR, transthyretin mediated; CV, cardiovascular; hATTR, hereditary transthyretin-mediated; wtATTR, wild-type transthyretin-mediated.

Results

Patient Demographics and Characteristics

- Responses from 27 patients with wtATTR amyloidosis were included
  - Patients had a mean age at diagnosis of 69.9 years
  - The majority of patients were male (89%) and White (85%)
  - Approximately one-quarter of patients had a mixed phenotype of both polyneuropathy and cardiomyopathy
- The majority of patients recorded received their diagnosis of wtATTR amyloidosis from a cardiologist (85%)
- Most patients (92%) had a genetic test to eliminate the possibility of hATTR amyloidosis, but 2 patients who self-reported a wtATTR amyloidosis diagnosis reported not receiving *TTR* genetic testing

Abbreviations: hATTR, hereditary transthyretin-mediated; TTR, transthyretin; wtATTR, wild-type transthyretin-mediated.

Results

Patient Demographics and Characteristics

Demographics and Characteristics	Subjects with wtATTR Amyloidosis (n=27)
Current age, years, mean	**72.5 years**
Age at diagnosis, years, mean (range)	69.9 (46–82)
Years since diagnosis, mean (range)	2.6 (0–11)
Male gender, n (%)	24 (89)
Ethnic background, n (%)	
White	23 (85)
Asian	1 (4)
Black or African American	2 (7)
Other[a]	1 (4)
Diagnoses of polyneuropathy and/or cardiomyopathy, n (%)	
Cardiomyopathy	17 (63)
Polyneuropathy	1 (4)
Both polyneuropathy and cardiomyopathy	7 (26)
I don't know/neither/blank	2 (7)
Genetic test, n (%)	
Yes	25 (92)
No	1 (4)
I don't know/blank	1 (4)
Age at genetic test, years, mean	70
Diagnosing physician, n (%)	
Cardiologist	23 (85)[b]
Hematologist	1 (4)
Amyloidosis specialist	3 (11)

[a]One participant responded 'American' to this question. [b]One patient specified their diagnosis was advanced heart failure diagnosed by a cardiologist.

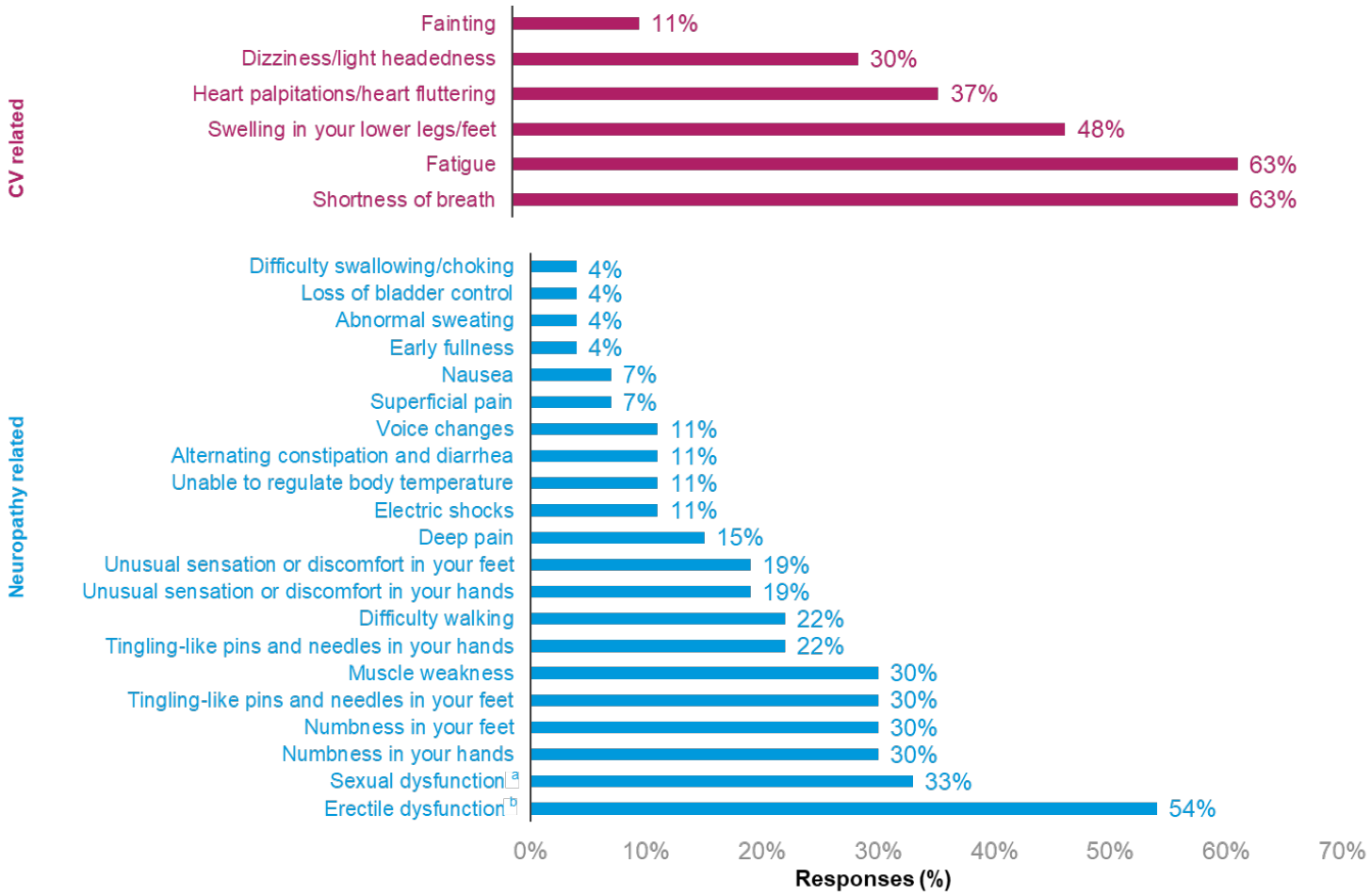
Abbreviations: wtATTR, wild-type transthyretin-mediated.

Results

Most Commonly Reported Signs/Symptoms

- Prior to diagnosis, patients reported experiencing both CV- and neuropathy-related signs and symptoms. The most commonly reported signs and symptoms potentially related to wtATTR amyloidosis were:
  - Fatigue (63%)
  - Shortness of breath (63%)
  - Erectile dysfunction (54% of males)
  - Swelling in the lower legs/feet (48%)

Prevalence of Signs/Symptoms (n=27)



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

Abbreviations: CV, cardiovascular; hATTR, hereditary transthyretin-mediated; wtATTR, wild-type transthyretin-mediated.

Results

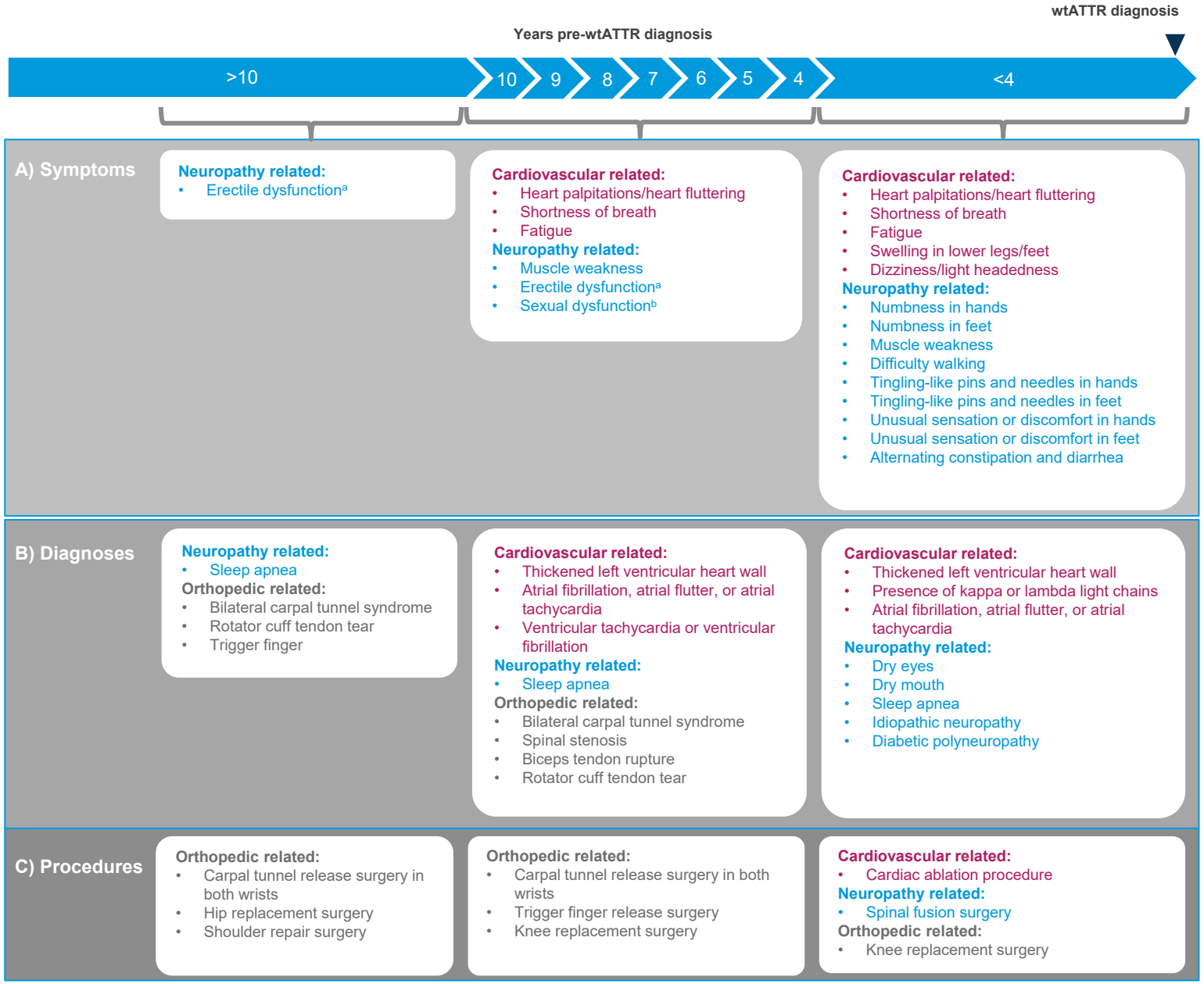
Timing of Signs/Symptoms Prior to wtATTR Amyloidosis Diagnosis

- The number of signs/symptoms reported by ≥10% of patients increased as patients approached diagnosis of wtATTR amyloidosis
  - Erectile dysfunction was the only sign or symptom reported by ≥10% of patients (male only) >10 years before diagnosis
  - At 4–10 and <4 years from diagnosis, ≥10% of patients reported other neuropathy-related signs/symptoms alongside CV-related symptoms

Abbreviations: ATTR, transthyretin mediated; CV, cardiovascular; hATTR, hereditary transthyretin-mediated; wtATTR, wild-type transthyretin-mediated.

Results

Occurrence of Signs/Symptoms, Other Diagnoses, and Procedures in ≥10% of Patients Prior to wtATTR Amyloidosis Diagnosis



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

Abbreviations: wtATTR, wild-type transthyretin-mediated.

Results

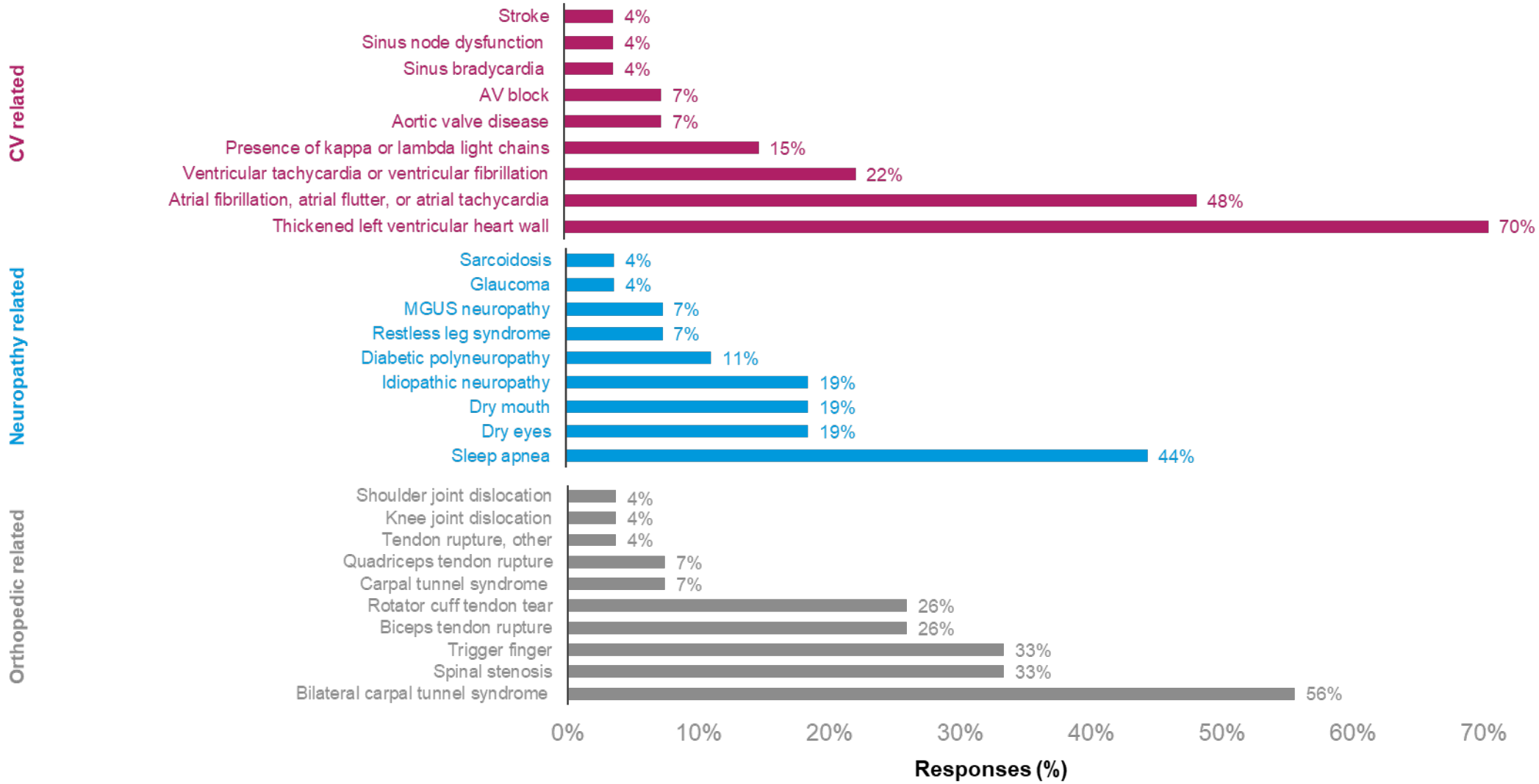
Other Diagnoses

- Overall, 28 CV-, neuropathy-, or orthopedic-related diagnoses associated with wtATTR amyloidosis were reported Thickened left ventricular heart wall (70%), atrial fibrillation, atrial flutter, or atrial tachycardia (48%), and ventricular tachycardia or ventricular fibrillation (22%) were the most common CV-related diagnoses reported
- Sleep apnea (44%) was the most commonly reported neuropathy-related diagnosis, followed by idiopathic neuropathy (19%), dry mouth (19%), and dry eyes (19%)
- Bilateral carpal tunnel syndrome (CTS) (56%), spinal stenosis (33%), trigger finger (33%), biceps tendon rupture (26%), and rotator cuff tendon tear (26%) were the most common orthopedic-related diagnoses reported
- While ≥10% of patients reported receiving diagnoses of heart arrhythmias and thickened heart walls 4–10 and 0–3 years pre-wtATTR amyloidosis diagnosis, at 4+ years from diagnosis the conditions reported were largely orthopedic (**Slide 36 Panel B**)
  - Specific orthopedic conditions (e.g., bilateral CTS) were diagnosed in ≥10% of patients 4–10+ years prior to wtATTR amyloidosis diagnosis
- Notably, ≥10% of patients reported receiving a diagnosis of sleep apnea >10 years prior to wtATTR amyloidosis diagnosis

Abbreviations: CTS, carpal tunnel syndrome; CV, cardiovascular; wtATTR, wild-type transthyretin-mediated.

Results

Prevalence of Other Diagnoses (n=27)

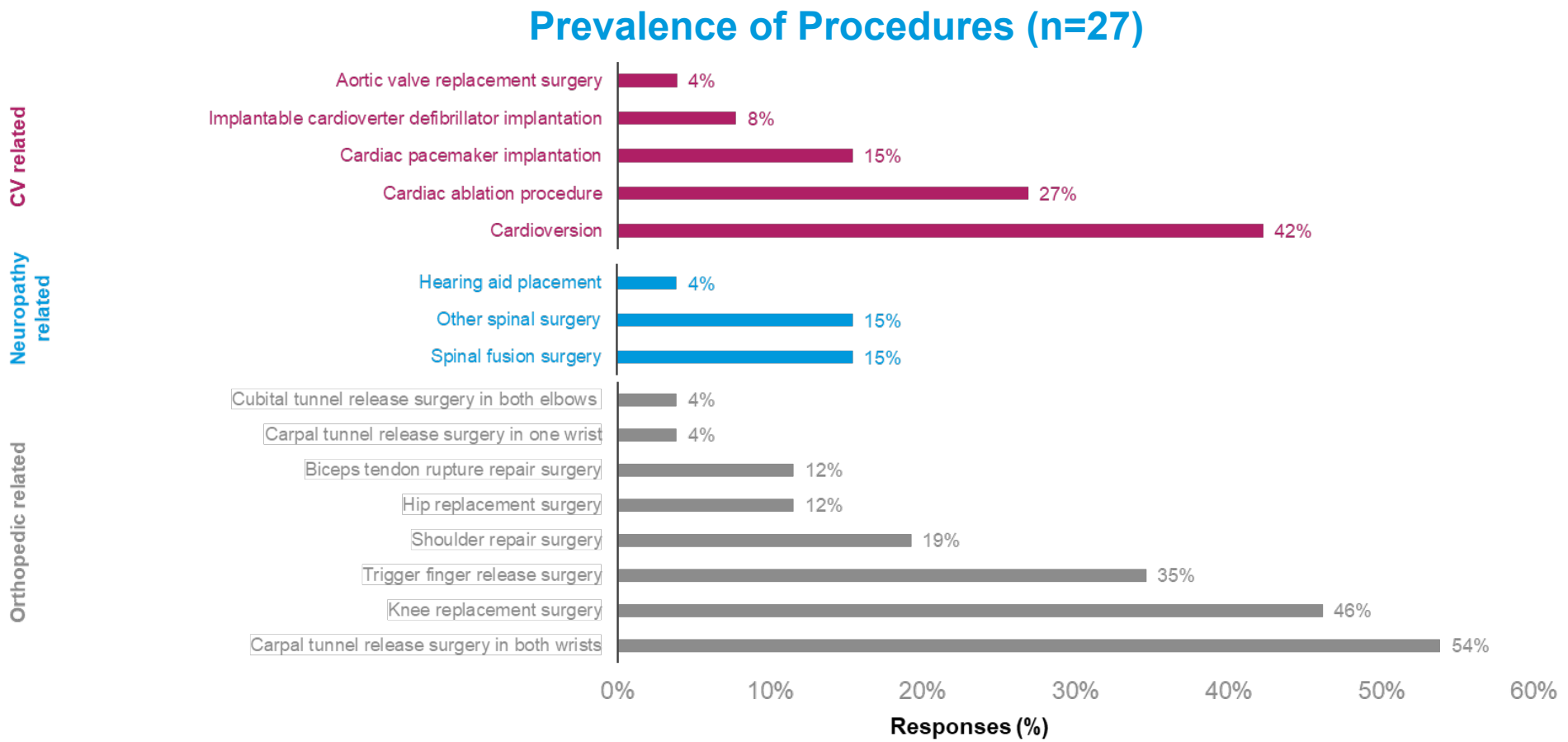


Abbreviations: AV, atrioventricular; CV, cardiovascular; MGUS, monoclonal gammopathy of undetermined significance.

Results

Procedures

- 14 different CV-, neuropathy-, or orthopedic-related procedures possibly related to wtATTR amyloidosis were reported
  CTS release surgery in both wrists was the most common procedure (54%)



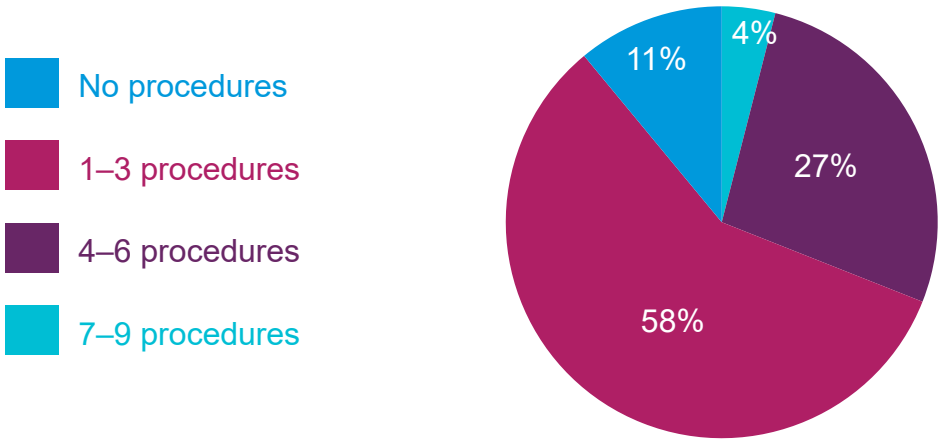
Abbreviations: CTS, carpal tunnel syndrome; CV, cardiovascular; wtATTR, wild-type transthyretin-mediated.

Results

Procedures

- 31% of patients reported experiencing ≥4 procedures prior to diagnosis of wtATTR amyloidosis Only 11% of patients reported no procedures prior to diagnosis of wtATTR amyloidosis
- Orthopedic-related procedures were recorded from >10 years prior to wtATTR diagnosis in ≥10% of patients (**Slide 36 Panel C**)

Number of Procedures (n=26[a])



[a]1 patient skipped this question.

Abbreviations: wtATTR, wild-type transthyretin-mediated.

Conclusions

- Patients reported neuropathy-, orthopedic-, and CV-related signs/symptoms highlighting the multisystem nature of wtATTR amyloidosis
- Patient responses to the online survey were consistent with previous studies showing extra-cardiac systems being impacted earlier in the course of wtATTR amyloidosis than the heart[1–3]
  - Neuropathy- and orthopedic-related signs/symptoms and diagnoses were more common earlier in the disease course, many occurring 4 to >10 years prior to wtATTR amyloidosis diagnosis
  - CV-related signs/symptoms and diagnoses occurred closer to wtATTR amyloidosis diagnosis
- Notably, CTS, the most commonly reported procedure in these patients, was performed in >10% of patients more than 10 years before their wtATTR amyloidosis diagnosis
- These results suggest that clinicians should implement specific strategies to facilitate diagnosis of wtATTR amyloidosis
  - Use of electronic medical records to guide clinical suspicion and work-up
  - Testing for amyloid (tissue sampling) during orthopedic procedures
  - Consideration of a patient's full medical history

Abbreviations: CTS, carpal tunnel syndrome; CV, cardiovascular; wtATTR, wild-type transthyretin-mediated.

References: 1. Lane et al. *Circulation* 2019;140:16–26; 2. M'bappe et al. *Best Pract Res Clin Rheumatol* 2012;26:459–75; 3. Gorevic ISA Congress 2020. Poster PT135.