History of Polyneuropathy and Musculoskeletal Manifestations in Patients with Transthyretin-Mediated Amyloidosis with Cardiomyopathy in APOLLO-B

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Conclusions

- **In patients with transthyretin amyloidosis (ATTR) with cardiomyopathy (ATTR-CM), signs and symptoms of polyneuropathy (PN) and musculoskeletal (MSK) manifestations occurred prior to a confirmed ATTR-CM diagnosis in >20% and >60% of all these patients, respectively**
- **The most frequently observed PN and MSK manifestations were erectile dysfunction and carpal tunnel syndrome, respectively**
- **Most PN and MSK manifestations occurred a median of at least 3 years prior to confirmed diagnosis of ATTR-CM**
- **Owing to the debilitating and fatal nature of ATTR-CM, identification of early signals and symptoms is crucial for prompt diagnosis and treatment**
  - **The evidence presented here demonstrates that PN and MSK manifestations may be early signals of impending cardiomyopathy that are potentially overlooked in patients with ATTR-CM**
  - **Multisystem clinical assessment and early identification of non-CM manifestations associated with ATTR may help in identifying patients prior to worsening disease severity**

Introduction

Transthyretin Amyloidosis

- ATTR is an underdiagnosed, progressive, debilitating, and fatal disease[1,2]
- It is caused by accumulation of toxic transthyretin (TTR) amyloid fibrils in multiple organs and tissues, including the nerves, heart, gastrointestinal tract, and MSK system[1–3]
  - The two types of ATTR are hereditary (ATTRv), in which variants in the *TTR* gene result in misfolded TTR protein, and wild-type (ATTRwt), in which wild-type TTR protein misfolds without a variant in the gene[1]
- Many patients with ATTR develop a mixed phenotype of both PN and CM, with PN and MSK manifestations occurring first, well before a confirmed diagnosis of ATTR-CM[4–6]

PN and MSK Manifestations Associated with ATTR

- PN manifestations associated with ATTR-CM include autonomic dysfunction, pain, numbness, walking disability, and erectile dysfunction[6]
- MSK manifestations include carpal tunnel syndrome, spinal stenosis, biceps tendon rupture, osteoarthritis, and trigger finger/finger tenosynovitis[6,7]
- Identifying PN and MSK manifestations could play an important role in early diagnosis and referral to allow for timely treatment

Objective

- To evaluate the occurrence of PN and MSK manifestations prior to a confirmed diagnosis of ATTR-CM in patients enrolled in APOLLO-B (NCT03997383)

Methods

APOLLO-B

- APOLLO-B is a multicenter, international, randomized, placebo-controlled, Phase 3 study that assessed the safety and efficacy of patisiran in patients with ATTR (ATTRwt and ATTRv)-CM in a 12-month double-blind period followed by an ongoing open-label extension[8]
  - Patients enrolled in the trial were aged 18–85 years of age with a diagnosis of ATTR-CM, defined as TTR amyloid deposition on tissue biopsy or fulfilling validated non-biopsy diagnostic criteria for ATTR-CM; evidence of cardiac involvement by echocardiography with an end-diastolic interventricular septal wall thickness >12 mm; and a medical history of heart failure[8]

Analysis of PN and MSK Manifestations Prior to a Confirmed Diagnosis of ATTR-CM

- Baseline disease characteristics and medical history collected during the screening period from APOLLO-B were analyzed in the overall study population (pooled across treatment arms) and separately in the ATTRwt and ATTRv subgroups:
- Medical history events were coded using Medical Dictionary for Regulatory Activities version 23.0
- The prevalence of PN and MSK manifestations in patients' medical histories prior to diagnosis of ATTR-CM was summarized descriptively
- Time from event onset to confirmed ATTR-CM diagnosis was summarized using descriptive statistics:
  - If a patient had several occurrences of an event in the medical history, the earliest time of onset was used
  - If a medical history event had an onset date that was missing the month or day, it was imputed to the earliest possible date
- Only events occurring in >5% of patients are reported

Results

Baseline Demographics and Disease Characteristics

- Data from 359 patients were included in the analysis, of whom 288 (80.2%) had ATTRwt and 71 (19.8%) had ATTRv
- Median age was 76 years, and the majority of patients were male (**Table 1**)
- At baseline, most patients were in ATTR National Amyloidosis Centre (NAC) stage 1, had a PN disability (PND) score of 0, and were in New York Heart Association (NYHA) Class II (**Table 1**)

Table 1. Baseline Demographics and Disease Characteristics

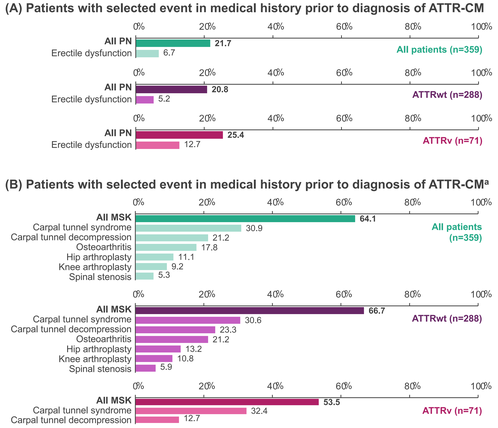
Parameter	All patients (N=359)
Age, years, median (range)	76 (41–85)
Male sex, n (%)	321 (89.4)
ATTRwt, n (%)	288 (80.2)
Time since diagnosis of ATTR, years, median (range)	0.5 (0–10)
NYHA Class,[a] n (%)	
Class I	25 (7.0)
Class II	306 (85.2)
Class III	28 (7.8)
ATTR NAC stage,[b] n (%)	
Stage 1	244 (68.0)
Stage 2	91 (25.3)
Stage 3	24 (6.7)
PND score, n (%)	
0: no impairment	205 (57.1)
I: preserved walking, with sensory disturbances	118 (32.9)
II: impaired walking without need for a stick or crutches	36 (10.0)
IIIa: one stick or crutch required for walking/IIIb: two sticks or crutches required for walking	0
IV: requires cane or stick to walk or is wheelchair bound	0

[a]Class 1, defined as no symptoms, ordinary physical activity does not cause fatigue or dyspnea; Class 2, defined as symptoms with ordinary physical activity; walking or climbing stairs rapidly, walking uphill, walking or stair-climbing after meals, in cold weather, in wind, or when under emotional stress causes undue fatigue or dyspnea; Class III, defined as symptoms with less than ordinary physical activity; walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea; [b]Patients are stratified into prognostic categories using the serum biomarkers NT-proBNP and eGFR. Patients are categorized as follows: stage 1 (lower risk): NT-proBNP ≤3000 ng/L and eGFR ≥45 mL/min/1.73 m^2; stage 2 (intermediate risk): all other patients not meeting criteria for stages 1 or 3; stage 3 (higher risk): NT-proBNP >3000 ng/L and eGFR <45 mL/min/1.73 m^2.

Prevalence of PN and MSK Manifestations in Medical Histories of Patients with ATTR-CM

- In the overall APOLLO-B study population, 21.7% of patients had events coded to PN in their medical history prior to ATTR-CM diagnosis, with similar proportions in the ATTRwt (20.8%) and ATTRv (25.4%) subgroups (**Figure 1**)
  - Erectile dysfunction was the most common PN manifestation in the overall population (6.7%)
- MSK manifestations prior to ATTR-CM diagnosis were found in the medical histories of 64.1% of all patients, with a slightly higher proportion in patients with ATTRwt vs ATTRv (66.7% vs 53.5%, respectively) (**Figure 1**)
  - The most common MSK manifestations were carpal tunnel syndrome (30.9%), carpal tunnel decompression (21.2%), and osteoarthritis (17.8%)

Figure 1. PN (A) and MSK (B) Medical History Events Prior to Diagnosis of ATTR-CM (Events Occurring in >5% of Patients)

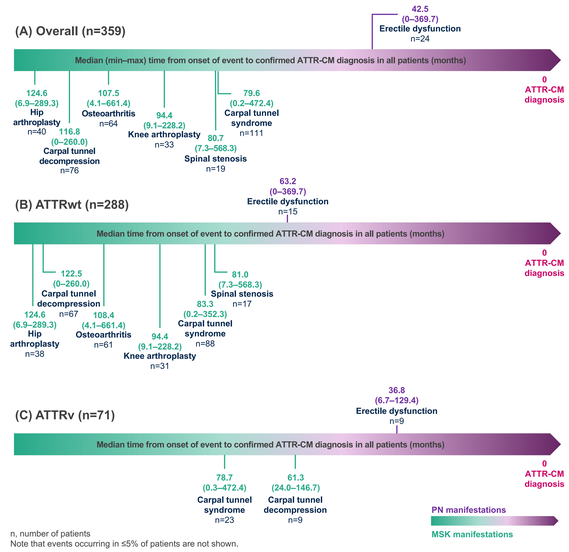


[a]Events occurring in ≤5% of patients are not shown

Time from Event Onset to Confirmed Diagnosis of ATTR-CM

- PN manifestations (any) occurred a median (range) of 40.5 (0–714.2) months prior to a confirmed diagnosis of ATTR-CM
  - Erectile dysfunction was the only PN manifestation reported in >5% of patients, with median (range) time of onset 42.5 (0–369.7) months prior to ATTR-CM diagnosis (**Figure 2A**)
  - Other PN manifestations in ≤5% of patients who had early onset included Raynaud's syndrome (median 237.5 [4.6–688.4] months; n=3) and orthostatic hypotension (median 10.4 [2.5–61.0] months; n=7)
- MSK manifestations (any) generally presented earlier than PN symptoms, with a median (range) onset of 138.6 (0.3–697.6) months prior to a confirmed diagnosis of ATTR-CM
  - Hip arthroplasty (median [range] 124.6 [6.9–289.3]) and carpal tunnel decompression (116.8 months [0–260.0]) were among the earliest occurring MSK manifestations, presenting up to a median of 10 years prior to diagnosis of ATTR-CM (**Figure 2A**)
- The timelines for onset of PN and MSK manifestations in patients with ATTRwt and ATTRv are shown in **Figure 2B and 2C**

Figure 2. Median Time from PN and MSK Manifestation Onset to Diagnosis of ATTR-CM (Events Occurring in >5% of Patients)



n, number of patients
Note that events occurring in ≤5% of patients are not shown.

Limitations

- Medical histories were limited to medical records/patient reports in APOLLO-B and not based on a targeted questionnaire or comprehensive clinical evaluation
  - Distinguishing whether the manifestations detected in the medical history are related to or caused by ATTR or comorbidities is challenging
- Conditions captured in this analysis may not be inclusive of all manifestations related to ATTR
- Further research to replicate these findings in larger cohorts may help to confirm these results

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Disclaimer: Patisiran is not approved for the treatment of ATTR-CM in the US, but ANSM has granted approval for the compassionate use of patisiran in France for patients with ATTR-CM failing tafamidis 61 mg.
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Abbreviations: ATTR, transthyretin amyloidosis; ATTR-CM, transthyretin amyloidosis with cardiomyopathy; ATTRv, hereditary transthyretin amyloidosis, v for variant; ATTRwt, wild-type hereditary transthyretin amyloidosis; eGFR, estimated glomerular filtration rate; MedDRA, Medical Dictionary for Regulatory Affairs; MSK, musculoskeletal; n, number of patients; NAC, National Amyloidosis Centre; NT-proBNP, *N*-terminal prohormone B-type natriuretic peptide; NYHA, New York Heart Association; PN, polyneuropathy; PND, polyneuropathy disability; TTR, transthyretin.
References: 1. Ruberg et al. *J Am Coll Cardiol* 2019;73:2872–92. 2. Maurer et al. *J Am Coll Cardiol* 2016;68:161–72; 3. Adams et al. *Nat Rev Neurol* 2019;15:387–404; 4. Adams et al. *N Engl J Med* 2018;379:11–21; 5. Rapezzi et al. *Eur Heart J* 2013;34:520–8; 6. Nativi-Nicolau et al. *Heart Fail Rev* 2022;27:785–793; 7. Yanagisawa et al. *Amyloid* 2016;23:26–32; 8. Maurer et al. *N Engl J Med* 2023;389:1553–65.
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